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| (54) Title: FIBRINOGEN RECEPTOR ANTAGONISTS | | |
| (57) Abstract Novel fibrinogen receptor antagonists of the formula: X-Y-Z-Aryl-A-B are provided in which the claimed compounds exhibit fibrinogen receptor antagonist activity, inhibit platelet aggregation and are therefore useful in modulating thrombus formation. | | |

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TITLE OF THE INVENTION
FIBRINOGEN RECEPTOR ANTAGONISTS

BACKGROUND OF THE INVENTION

5 The invention relates generally to modulating cRe:
 Patenthe binding of fibrinogen and other proteins to blood
platelets, and inhibiting the aggregation of blood platelets specifically to
the IIb/IIIa fibrinogen receptor site. Fibrinogen is a glycoprotein
present in blood plasma that participates in platelet aggregation and in
10 fibrin formation. Platelets are anucleated cells, found in the blood of all
mammals, that also participate in blood coagulation. Interaction of
fibrinogen with the IIb/IIIa receptor site is known to be essential for
normal platelet function.

15 When a blood vessel is damaged by an injury or other
causative factor, platelets adhere to the disrupted subendothelial surface.
The adherent platelets subsequently release biologically active
constituents and aggregate. Aggregation is initiated by the binding of
agonists, such as thrombin, epinephrine, or ADP to specific platelet
membrane receptors. Stimulation by agonists results in exposure of
20 latent fibrinogen receptors on the platelet surface, and binding of
fibrinogen to the glycoprotein IIb/IIIa receptor complex.

 Attempts have been made to use natural products and
synthetic peptides to determine the mechanism of adhesion and platelet
aggregation. For example, Rouslahti and Pierschbacher in Science, 238,
25 491-497 (1987), describe adhesive proteins such as fibronectin,
vitronectin, osteopontin, collagens, thrombospondin, fibrinogen, and
von Willebrand factor that are present in extracellular matrices and in
blood. These proteins contain the tripeptide sequence arginine-glycine-
aspartic acid (RGD) as their glycoprotein IIb/IIIa recognition site.
30 These arginine-glycine-aspartic acid containing tripeptides are
recognized by at least one member of a family of structurally related
receptors, integrins, which are heterodimeric proteins with two
membrane-spanning subunits. The authors state that the conformation

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of the tripeptide sequence in the individual proteins may be critical to recognition specificity.

Cheresh in Proc. Nat'l Acad. Sci. U.S.A., 84, 6471-6475, (1987), describes an Arg-Gly-Asp directed adhesion receptor expressed by human endothelial cells that is structurally similar to the IIb/IIIa complex on platelets but is antigenically and functionally distinct. This receptor is directly involved in endothelial cell attachment to fibrinogen, von Willebrand factor, and vitronectin.

Pierschbacher and Rouslahti, in J. of Biol. Chem., 262, (36), 17294-17298 (1987) hypothesized that the Arg-Gly-Asp sequence alone would be a sufficient signal for receptor recognition and binding and that, therefore, the conformation of the tri-peptide sequence would be determinative. Various synthetic peptides were produced and the authors concluded that the stereochemical conformation of Arg-Gly-Asp as influenced by enantiomeric substitutions or additions to this sequence significantly influenced receptor-ligand interaction. The authors further showed that cyclization of a decapeptide by forming a disulfide bridge between non-terminal residues Pen and Cys, rendered the peptide much less effective at inhibiting attachment to fibronectin.

In Proc. Nat'l Acad. Sci. U.S.A., 81, 5985-5988 (1984), the same authors describe tetrapeptide variants of the cell recognition site of fibronectin that retain attachment-promoting activity. Peptides having a tetrapeptide recognition site are described in U.S. Pat. Nos. 4,589,881 and 4,614,517. A number of large polypeptide fragments in the cell-binding domain of fibronectin have cell-attachment activity. For example, see U.S. Pat. Nos. 4,517,686, 4,661,111 and U.S. Pat. No. 4,578,079.

Ruggeri et al., Proc. Nat'l Acad. Sci. U.S.A., 83, 5708-5712 (1986) explore a series of synthetic peptides designed in lengths to 16 residues, that contain RGD and a valine attached to the aspartic acid residue of RGD that inhibit fibrinogen binding to platelets. See also Koczewiak et al., Biochem. 23, 1767-1774 (1984); Ginsberg et al., J. Biol. Chem. 260(7), 3931-3936 (1985); and Haverstick et al., Blood

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66(4), 946-952 (1985). Other inhibitors are disclosed in Eur. Pat. App. Nos. 275,748 and 298,820.

A number of low molecular weight polypeptide factors have been isolated from snake venom. These factors apparently have high affinity for the gpIIb/IIIa complex. For example, Huang *et al.*, J. Biol. Chem., 262, 16157-16163 (1987); Huang *et al.*, Biochemistry 28, 661-666 (1989) describe the primary structure of the venom trigramin which is a 72 amino acid polypeptide that contains the RGD subunit. Echistatin is another venom which has high affinity for the gpIIb/IIIa complex. This polypeptide contains 49 amino acids and has the RGD subunit and various disulfide bridges. Gan *et al.*, J. Biol. Chem., 263, 19827-19832 (1988). See also, Dennis *et al.*, Proc. Nat'l Acad. Sci. USA, 87, 2471-2475 (1989). However, these snake venom factors also have high affinity for other members of the adhesive protein receptor family including the vitronectin and fibronectin receptors so are not selective for the gpIIb/IIIa complex.

While it is known that the tripeptide sequence Arg-Gly-Asp is present in certain polypeptides that can duplicate or inhibit the cell attachment-promoting effects of fibronectin and vitronectin, the tripeptide Arg-Gly-Asp has low activity. At present, there is little understanding of how other amino acids coupled to this sequence influence binding specificity. U.S. Pat. No 5,023,233, assigned to Merck & Co., Inc., discloses small cyclic hexapeptides which contain the sequence Arg-Gly-Asp and are useful platelet aggregation inhibitors. U.S. Pat. No. 5,037,808 discloses the use of indolyl platelet-aggregation inhibitors which are believed to act by antagonizing interactions between fibrinogen and/or extracellular matrix proteins and the platelet gpIIb/IIIa receptor. U.S. Pat. No. 5,037,808 discloses guanidino peptide mimetic compounds that retain an Asp residue which inhibit platelet aggregation. The application PCT/US90/02746 describes the use of antibody-polypeptide conjugates wherein said polypeptides contain the Arg-Gly-Asp (RGD) sequence.

The application PCT/US91/00564 discloses the use of large cyclic peptides containing RGD flanked by proline residues which are

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platelet aggregation inhibitors. The application PCT/US90/03788 discloses small cyclic platelet aggregation inhibitors which are synthetic cyclic pentapeptides containing the tripeptide sequence Arg-Gly-Asp and a thioether linkage in the cycle. The application PCT/US90/05367
5 published May 2, 1991 also discloses the use of peptides and pseudopeptides such as N-amidino-piperidine-3-carboxylglycyl-L-aspartyl-L-valine that inhibit platelet aggregation and thrombus formation in mammalian blood. The application Eur. Pat. App. No. 91103462.7 discloses linear compounds which can include internal
10 piperazinyl or piperidinyl derivatives. Eur. Pat. App. No. 91300179.8, assigned to Merck & Co., Inc., and published on July 17, 1991 discloses linear polypeptide-fibrinogen receptor antagonists. Eur. Pat. App. No. 90101404.3 discloses compounds of the $R^1-A(W)_a-X(CH_2)_b-(Y)_c-B-Z-COOR$ wherein R^1 is a guandidino or amidino moiety and A and B are chosen from specific monosubstituted aryl or heterocyclic moieties.
15

While a multitude of compounds or peptide analogs believed to inhibit platelet aggregation by inhibiting binding to a blood platelet by fibrinogen are known, the present invention provides novel
20 fibrinogen receptor antagonists that have significant binding activity and are, therefore, useful for the reasons stated herein. A number of very serious diseases and disorders involve hyperthrombotic complications which lead to intravascular thrombi and emboli. Myocardial infarction, stroke, phlebitis and a number of other serious conditions create the
25 need for novel and effective fibrinogen receptor antagonists.

SUMMARY OF THE INVENTION

The invention is a fibrinogen receptor antagonist of the formula:

30



and the pharmaceutically acceptable salts thereof wherein:

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Aryl is a 6-membered monocyclic aromatic ring system containing 0, 1, 2, 3, or 4 N atoms and either unsubstituted or substituted with R⁵;

5

X is $\begin{matrix} & \text{NR}^2 & \text{NR}^3 \\ & | & | \\ -\text{NR}^1\text{R}^2, & -\text{NR}^1\text{-C-R}^1, & -\text{C-NHR}^4, \end{matrix}$

10

$\begin{matrix} & \text{NR} \\ & | \\ -\text{NR}^1\text{-C-NR}^3\text{R}^4, \end{matrix}$ or a 4- to 10- membered mono- or polycyclic aromatic or nonaromatic ring system and containing 0, 1, 2, 3 or 4 heteroatoms selected from N, O and S and either unsubstituted or substituted with R¹, R², R³ or R⁴, wherein R¹, R², R³ and R⁴ are independently selected from the group consisting of hydrogen, C₁-10 alkyl, C₃-8 cycloalkyl, aryl C₀-8 alkyl, amino C₀-8 alkyl, C₁-3 acylamino C₀-8 alkyl, C₁-6 alkylamino C₀-8 alkyl, C₁-6 dialkylamino C₀-8 alkyl, C₁-4 alkoxy C₀-6 alkyl, carboxy C₀-6 alkyl, C₁-3 alkoxycarbonyl C₀-6 alkyl, carboxy C₀-6 alkyloxy, or hydroxy C₀-6 alkyl;

25

Y is

30

C₀-8 alkyl, C₄-10 cycloalkyl, C₀-8 alkyl-NR³-CO-C₀-8 alkyl, C₀-8 alkyl-CONR³-C₀-8 alkyl, C₀-8 alkyl-O-C₀-8 alkyl, C₀-8 alkyl-S(O_n)-C₀-8 alkyl, (CH₂)₀-8aryl(CH₂)₀-8, (CH₂)₀-6aryl-SO_n-(CH₂)₀-8aryl-CO-(CH₂)₀-8, (CH₂)₀-6aryl-SO₂-(CH₂)₀-6,

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$(\text{CH}_2)_{0-6}\text{-NR}^3\text{-(CH}_2)_{0-6}$,
 $(\text{CH}_2)_{0-6}\text{-aryl-CH(OH)-(CH}_2)_{0-6}$,
 $(\text{CH}_2)_{0-8}\text{aryl-CONH-(CH}_2)_{0-8}$,
 $\text{C}_{0-8}\text{ alkyl-SO}_2\text{-NR}^3\text{-C}_{0-8}\text{ alkyl}$,
 $\text{C}_{0-8}\text{ alkyl-CO-C}_{0-8}\text{ alkyl}$, or
 $\text{C}_{0-8}\text{ alkyl-CH(OH)-C}_{0-8}\text{-alkyl}$

where n is an integer from 0-2;

Z and A are independently chosen from

$(\text{CH}_2)_m$, $(\text{CH}_2)_m\text{O(CH}_2)_n$,

$(\text{CH}_2)_m\overset{\text{O}}{\underset{\text{O}}{\text{C}}}\text{NR}^3(\text{CH}_2)_n$, $(\text{CH}_2)_m\overset{\text{O}}{\underset{\text{S}}{\text{NR}^3\text{C}}}(\text{CH}_2)_n$,

$(\text{CH}_2)_m\text{C(CH}_2)_n$, $(\text{CH}_2)_m\text{C(CH}_2)_n$, $(\text{CH}_2)_m\text{SO}_2(\text{CH}_2)_n$,
 $(\text{CH}_2)_m\text{S(CH}_2)_n$, $(\text{CH}_2)_m\text{SO(CH}_2)_n$,
 $(\text{CH}_2)_m\text{SO}_2\text{NR}^3(\text{CH}_2)_n$, $(\text{CH}_2)_m\text{NR}^3\text{SO}_2(\text{CH}_2)_n$,
 $(\text{CH}_2)_m\text{CR}^3=\text{CR}^4(\text{CH}_2)_n$, $(\text{CH}_2)_m\text{C}=\text{C(CH}_2)_n$, and
 $(\text{CH}_2)_m\text{CH(OH)(CH}_2)_n$,

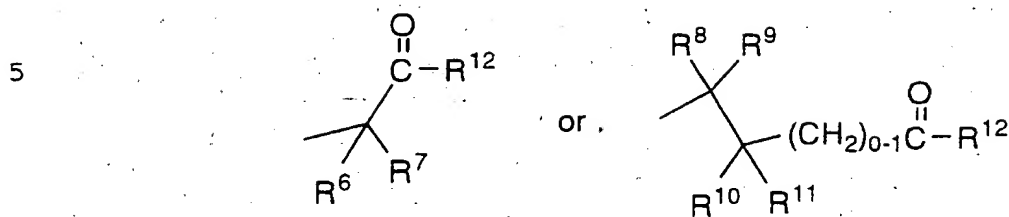
where m and n are integers independently chosen from 0-6; provided
 that when A is $(\text{CH}_2)_m$, the Aryl ring, bonded by Z and A, must contain
 at least one heteroatom;

R⁵ is

hydrogen
 C₁₋₆ alkyl,
 C₀₋₆ alkylcarboxy C₀₋₆ alkyl,
 C₀₋₆ alkyloxy C₀₋₆ alkyl,
 hydroxy C₀₋₆ alkyl,
 aryl C₀₋₆ alkyl, or
 halogen;

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B is



wherein R6, R7, R8, R9, R10, and R11 are independently chosen from:

- hydrogen, fluorine, hydroxy C1-6 alkyl, carboxy C0-6 alkyl,
- 15 C1-8 alkyl, hydroxyl, C1-6 alkyloxy, aryl C0-6alkyloxy, C3-8 cycloalkyl,
- aryl C0-6 alkyl, C1-6 alkylcarbonyloxy,
- C0-6 alkylamino C0-6 alkyl, aryl C0-6 alkylamino C0-6 alkyl, aryl C0-6 alkylcarbonyloxy,
- 20 C0-6 dialkylamino C0-6 alkyl, C1-6 alkylamino-carbonyloxy,
- C1-8 alkylsulfonylamino C0-6 alkyl,
- aryl C0-6 alkylsulfonylamino C0-6 alkyl,
- C1-8 alkyloxycarbonylamino C0-8 alkyl,
- 25 aryl C0-8 alkyloxycarbonylamino C0-8 alkyl,
- C1-8 alkylcarbonylamino C0-6 alkyl,
- aryl C0-6 alkylcarbonylamino C0-6 alkyl,
- C0-8 alkylaminocarbonylamino C0-6 alkyl,
- aryl C0-8 alkylaminocarbonylamino C0-6 alkyl,
- 30 C0-8 alkylaminosulfonylamino C0-6 alkyl,
- aryl C0-8 alkylaminosulfonylamino C0-6 alkyl,
- C1-8 alkylsulfonyl C0-6 alkyl,
- aryl C0-6 alkylsulfonyl C0-6 alkyl,
- C1-6 alkylcarbonyl C0-6 alkyl,
- aryl C0-6 alkylcarbonyl C0-6 alkyl,

C0-8 alkylaminocarbonyl C0-8 alkyl,
aryl C0-8 alkylaminocarbonyl C0-8 alkyl,
C0-8 alkylaminosulfonyl C0-8 alkyl, and
aryl C0-8 alkylaminosulfonyl C0-8 alkyl,

wherein groups may be unsubstituted or substituted with one or more
substituents selected from R¹ and R²; and

R¹² is chosen from

hydroxy,
C1-8 alkyloxy,
aryl C0-6 alkyloxy,
C1-8 alkylcarbonyloxy C1-4 alkyloxy,
aryl C1-8 alkylcarbonyloxy C1-4 alkyloxy, and
an L- or D-amino acid joined by an amide linkage and
wherein the carboxylic acid moiety of said amino acid is as
the free acid or is esterified by C1-6 alkyl.

When substituent R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹,
R¹⁰, R¹¹, R¹², X or Y includes the definition CO, (e.g. aryl CO alkyl),
the group modified by CO is not present in the substituent.

A preferred embodiment of the present invention is

X-Y-Z-Aryl-A-B

and the pharmaceutically acceptable salts thereof wherein:

Aryl is a 6-membered aromatic ring system containing 0, 1, 2, or 3 N
atoms;

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X is

NR² NR³

-NR¹R², -NR¹-C-R¹, -C-NHR⁴,
 NR²
 -NR¹-C-NR³R⁴, or a 4- to 10- membered mono- or
 polycyclic aromatic or nonaromatic ring system containing
 0, 1, 2, 3 or 4 heteroatoms selected from N, O and S and
 either unsubstituted or substituted with R¹, R², R³, or R⁴,
 wherein R¹, R², R³ and R⁴ are independently selected
 from the group consisting of hydrogen,
 C₁₋₁₀ alkyl, C₃₋₈ cycloalkyl,
 aryl C₀₋₈ alkyl,
 amino C₀₋₈ alkyl, C₁₋₃ acylamino C₀₋₈ alkyl,
 C₁₋₆ alkylamino C₀₋₈ alkyl,
 C₁₋₆ dialkylamino C₀₋₈ alkyl,
 C₁₋₄ alkoxy C₀₋₆ alkyl,
 carboxy C₀₋₆ alkyl, C₁₋₃ alkoxycarbonyl C₀₋₆
 alkyl,
 carboxy C₀₋₆ alkyloxy and
 hydroxy C₀₋₆ alkyl;

Y is

C₀₋₈ alkyl,
 C₀₋₈ alkyl-NR³-CO-C₀₋₈ alkyl,
 C₀₋₈ alkyl-CONR³-C₀₋₈ alkyl,
 C₀₋₈ alkyl-O-C₀₋₈ alkyl, C₀₋₈ alkyl aryl C₀₋₈ alkyl,
 C₀₋₈ alkyl-S(O_n)-C₀₋₈ alkyl,
 C₀₋₈ alkyl-SO₂-NR³-C₀₋₈ alkyl-, or
 C₀₋₈ alkyl-CO-C₀₋₈ alkyl-,

where n is an integer from 0-2;

Z and A are independently chosen from:

$(CH_2)_m$, $(CH_2)_mO(CH_2)_n$, $(CH_2)_mNR^3(CH_2)_n$,

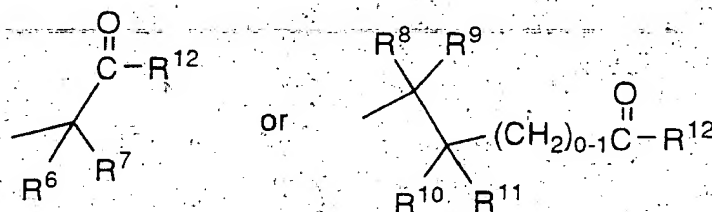
$(CH_2)_mC(=O)NR^3(CH_2)_n$, $(CH_2)_mNR^3C(=O)(CH_2)_n$,

$(CH_2)_mC(CH_2)_n$, $(CH_2)_mSO_2(CH_2)_n$,

$(CH_2)_mSO_2NR^3(CH_2)_n$, and $(CH_2)_mNR^3SO_2(CH_2)_n$,

where m and n are integers independently chosen from 0-6;
provided that when A is $(CH_2)_m$, the Aryl ring bonded by Z and A,
must contain at least one heteroatom;

B is



20 wherein R6, R7, R8, R9, R10 and R11 are independently chosen from:
hydrogen, fluorine

C1-8 alkyl,

C3-8 cycloalkyl,

25 aryl C0-6 alkyl,

C0-6 alkylamino C0-6 alkyl,

aryl C0-6 alkylamino C0-6 alkyl,

C0-6 dialkylamino C0-6 alkyl,

C1-8 alkylsulfonylamino C0-6 alkyl,

30 aryl C0-6 alkylsulfonylamino C0-6 alkyl,

C1-8 alkyloxycarbonylamino C0-8 alkyl,

aryl C0-8 alkyloxycarbonylamino C0-8 alkyl,

C1-8 alkylcarbonylamino C0-6 alkyl,

aryl C0-6 alkylcarbonylamino C0-6 alkyl,

C0-8 alkylaminocarbonylamino C0-6 alkyl,

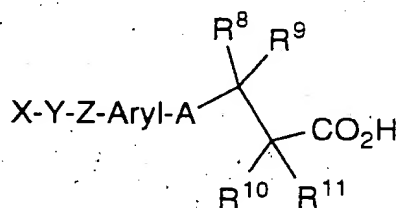
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aryl C0-8 alkylaminocarbonylamino C0-6 alkyl,
 C0-8 alkylaminosulfonylamino C0-6 alkyl,
 aryl C0-8 alkylaminosulfonylamino C0-6 alkyl,
 C1-6 alkylsulfonyl C0-6 alkyl,
 aryl C0-6 alkylsulfonyl C0-6 alkyl,
 C1-6 alkylcarbonyl C0-6 alkyl, and
 aryl C0-6 alkylcarbonyl C0-6 alkyl; and

R¹² is chosen from:

hydroxy,
 C1-8 alkyloxy,
 aryl C0-6 alkyloxy,
 C1-8 alkylcarbonyloxy C1-4 alkyloxy, and
 aryl C1-8 alkylcarbonyloxy C1-4 alkyloxy.

A more preferred embodiment of the present invention is:



and the pharmaceutically acceptable salts thereof wherein:

Aryl is a 6-membered monocyclic aromatic ring system containing 0, 1 or 2 N atoms;

NR³

X is -NR¹R², -C-NHR⁴, or a 4- to 8-membered nonaromatic ring system containing 0, 1, 2 or 3 heteroatoms selected from N and O wherein R¹, R², R³

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and R⁴ are independently selected from the group consisting of hydrogen, C₁₋₁₀ alkyl, aryl C₀₋₈ alkyl, carboxy C₀₋₆ alkyl, hydroxy C₀₋₆ alkyl, amino C₀₋₈ alkyl, or C₁₋₆ alkylamino C₀₋₈ alkyl;

Y is C₀₋₈ alkyl, C₀₋₈ alkyl-NR³-CO-C₀₋₈ alkyl, C₀₋₈ alkyl-CONR³-C₀₋₈ alkyl, C₀₋₈ alkyl-O-C₀₋₈ alkyl, C₀₋₈ alkyl-S(O_n)-C₀₋₈ alkyl, or C₀₋₈ alkyl aryl C₀₋₈ alkyl;

Z and A are independently chosen from

$$\begin{array}{c} \text{O} \\ | \\ (\text{CH}_2)_m, (\text{CH}_2)_m\text{C}(\text{CH}_2)_n, (\text{CH}_2)_m\text{O}(\text{CH}_2)_n, \\ (\text{CH}_2)_m\text{SO}_2(\text{CH}_2)_n, \text{ and } (\text{CH}_2)_m\text{CONR}^3(\text{CH}_2)_n, \end{array}$$

wherein m and n are integers independently chosen from 0-6 and provided that when A is (CH₂)_m, the Aryl ring bounded by Z and A, must contain at least one heteroatom; and

R⁸, R⁹, R¹⁰ and R¹¹ are independently chosen from

hydrogen, fluorine, C₁₋₈ alkyl, C₃₋₈ cycloalkyl, aryl C₀₋₆ alkyl, C₀₋₆ alkylamino C₀₋₆ alkyl, C₀₋₆ dialkylamino C₀₋₆ alkyl,

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5 C1-8 alkylsulfonylamino C0-6 alkyl,
aryl C0-6 alkylsulfonylamino C0-6 alkyl,
C1-8 alkyloxycarbonylamino C0-8-alkyl,
aryl C0-8 alkyloxycarbonylamino C0-8 alkyl,
10 C1-8 alkylcarbonylamino C0-6 alkyl,
aryl C0-6 alkylcarbonylamino C0-6 alkyl,
C0-8 alkylaminocarbonylamino C0-6 alkyl,
aryl C0-8 alkylaminocarbonylamino C0-6 alkyl,
15 C0-8 alkylaminosulfonylamino C0-6 alkyl,
aryl C0-8 alkylaminosulfonylamino C0-6 alkyl,
C1-6 alkylsulfonyl C0-6 alkyl,
aryl C0-6 alkylsulfonyl C0-6 alkyl,
C1-6 alkylcarbonyl C0-6 alkyl, and
20 aryl C0-6 alkylcarbonyl C0-6 alkyl

DETAILED DESCRIPTION OF THE INVENTION

20 The term "pharmaceutically acceptable salts" shall mean non-toxic salts of the compounds of this invention which are generally prepared by reacting the parent compound with a suitable organic or inorganic acid or base. Representative salts include the following salts: Acetate, benzenesulfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate, bromide, calcium edetate, camsylate, carbonate, chloride, clavulanate, citrate, dihydrochloride, edetate, edisylate, estolate, esylate, 25 fumarate, gluceptate, gluconate, glutamate, glycolylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynapthoate, iodide, isothionate, lactate, lactobionate, laurate, malate, maleate, mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, oleate, oxalate, pamaote, 30 palmitate, panthothenate, phosphate/diphosphate, polygalacturonate, salicylate, stearate, subacetate, succinate, tannate, tartrate, teoclate, tosylate, triethiodide, valerate.

The term "pharmaceutically effective amount" means that amount of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, system or animal that is being sought by

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a researcher or clinician. The term "anti-coagulant" shall include heparin, and warfarin. The term "thrombolytic agent" shall include streptokinase and tissue plasminogen activator. The term "platelet anti-aggregation agent" shall include aspirin and dipyridamole.

5 The term "alkyl" means straight or branched alkane, alkene or alkyne. The term "alkoxy" includes an alkyl portion where alkyl is as defined above.

10 The terms "arylalkyl" and "alkylaryl" include an alkyl portion where alkyl is as defined above and to include an aryl portion where aryl is as defined above. The C_{0-n} or C_{1-n} designation where n may be an integer from 1-10 or 2-10 respectively refers to the alkyl component of the arylalkyl or alkylaryl unit.

15 The term "halogen" includes fluorine, chlorine, iodine and bromine.

Under standard nomenclature used throughout this disclosure, the terminal portion of the designated side chain is described first followed by the adjacent functionality toward the point of attachment. For example, a C₁₋₆ alkyl substituted with C₁₋₆ alkylcarbonylamino is equivalent to



25 The term "Aryl" is different from the term "aryl", wherein "Aryl" is defined in its broadest scope as a 6-membered monocyclic aromatic ring system containing 1, 2, 3 or 4 N atoms, and either unsubstituted or substituted. The term "aryl" is now defined to be a mono- or polycyclic ring system containing 0, 1, 2, 3, 4 or 5 heteroatoms chosen from N, O and S, comprised of 5- or 6- membered rings, either unsubstituted or substituted with substituents chosen from R¹ and R².

30 In the schemes and examples below, various reagent symbols have the following meanings:

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| | | |
|----|-----------------------------------|--|
| | BOC(Boc): | t-Butyloxycarbonyl. |
| | Pd/C: | Palladium on activated carbon catalyst. |
| | DEAD: | Diethylazodicarboxylate. |
| | DIAD: | Diisopropylazodicarboxylate. |
| 5 | DMF: | Dimethylformamide. |
| | DMSO: | Dimethylsulfoxide. |
| | CBZ: | Benzyloxycarbonyl. |
| | CH ₂ Cl ₂ : | Methylene chloride. |
| | CHCl ₃ : | chloroform. |
| 10 | EtOH: | ethanol. |
| | MeOH: | methanol. |
| | EtOAc: | ethyl acetate. |
| | HOAc: | acetic acid. |
| 15 | BOP: | Benzotriazol-1-yloxytris(dimethylamino)phosphonium, hexafluorophosphate. |
| | EDC: | 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide. |
| | Oxone: | potassium peroxymonosulfate. |
| | LDA: | Lithium diisopropylamide. |
| | CDI: | Carbonyldiimidazole. |
| 20 | NMM: | N-Methylmorpholine. |
| | DIPEA: | Diisopropylethylamine. |
| | TMSI: | Trimethylsilyliodide. |
| | TFA: | Trifluoroacetic acid. |
| 25 | py: | Pyridine. |

The compounds of the present invention can be administered in such oral forms as tablets, capsules (each of which includes sustained release or timed release formulations), pills, powders, granules, elixers, tinctures, suspensions, syrups, and emulsions.

30 Likewise, they may be administered in intravenous (bolus or infusion), intraperitoneal, subcutaneous, or intramuscular form, all using forms well known to those of ordinary skill in the pharmaceutical arts. An effective but non-toxic amount of the compound desired can be employed as an anti-aggregation agent.

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Compounds of the invention may be administered to patients where prevention of thrombosis by inhibiting binding of fibrinogen to the platelet membrane glycoprotein complex IIb/IIIa receptor is desired. They are useful in surgery on peripheral arteries (arterial grafts, carotid endarterectomy) and in cardiovascular surgery where manipulation of arteries and organs, and/or the interaction of platelets with artificial surfaces, leads to platelet aggregation and consumption. The aggregated platelets may form thrombi and thromboemboli. They may be administered to these surgical patients to prevent the formation of thrombi and thromboemboli.

Extracorporeal circulation is routinely used for cardiovascular surgery in order to oxygenate blood. Platelets adhere to surfaces of the extracorporeal circuit. Adhesion is dependent on the interaction between gpIIb/IIIa on the platelet membranes and fibrinogen adsorbed to the surface of the circuit. (Gluszko et al., Amer. J. Physiol., 252(H), 615-621 (1987)). Platelets released from artificial surfaces show impaired hemostatic function. Compounds of the invention may be administered to prevent adhesion.

Other applications of these compounds include prevention of thrombosis, thromboembolism and reocclusion during and after thrombolytic therapy and prevention of thrombosis, thromboembolism and reocclusion after angioplasty or coronary artery bypass procedures. They may also be used to prevent or modulate myocardial infarction.

The dosage regimen utilizing the compounds of the present invention is selected in accordance with a variety of factors including type, species, age, weight, sex and medical condition of the patient; the severity of the condition to be treated; the route of administration; the renal and hepatic function of the patient; and the particular compound or salt thereof employed. An ordinarily skilled physician or veterinarian can readily determine and prescribe the effective amount of the drug required to prevent, counter, or arrest the progress of the condition.

In the methods of the present invention, the compounds herein described in detail can form the active ingredient, and are

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typically administered in admixture with suitable pharmaceutical diluents, excipients or carriers (collectively referred to herein as "carrier" materials) suitably selected with respect to the intended form of administration, that is, oral tablets, capsules, elixers, syrups and the like, and consistent with convention pharmaceutical practices.

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic, pharmaceutically acceptable, inert carrier such as lactose, starch, sucrose, glucose, methyl cellulose, magnesium stearate, dicalcium phosphate, calcium sulfate, mannitol, sorbitol and the like; for oral administration in liquid form, the oral drug components can be combined with any oral, non-toxic, pharmaceutically acceptable inert carrier such as ethanol, glycerol, water and the like. Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn-sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. Disintegrators include, without limitation, starch methyl cellulose, agar, bentonite, xanthan gum and the like.

The compounds of the present invention can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

Compounds of the present invention may also be delivered by the use of monoclonal antibodies as individual carriers to which the compound molecules are coupled. The compounds of the present invention may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropyl-methacrylamide-phenol, polyhydroxy-

ethyl-aspartamide-phenol, or polyethyleneoxide-polylysine substituted with palmitoyl residues. Furthermore, the compounds of the present invention may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and cross linked or amphipathic block copolymers of hydrogels.

The compounds of the present invention can also be co-administered with suitable anti-coagulation agents or thrombolytic agents such as plasminogen activators or streptokinase to achieve synergistic effects in the treatment of various vascular pathologies. They may also be combined with heparin, aspirin, or warfarin.

Preferred compounds of the invention are selected from the group consisting of:

N-2-(4-Piperidinylethyl)-N'-(2-carboxyethyl)-1,3-benzenedicarboxamide;

N-2-(4-Piperidinylethyl)-N'-[3-(2-fluoro)propanoic-acid]-1,3-benzenedicarboxamide;

{N-2-(4-Piperidinylethyl)-N'-3-[3(R)-phenethylpropanoic acid]}-1,3-benzenedicarboxamide;

{N-[2-(4-Piperidinylethyl)-N'-3-[3(R)-indolylethylpropanoic acid]}-1,3-benzenedicarboxamide;

N-(4-Piperidinylmethyl)-N'-3-[2(S)-n-butylsulfonylaminopropionic acid]-1,3-benzenedicarboxamide;

N-(4-Piperidinylmethyl)-N'-[(2-carboxyethyl)-1,3-benzenedicarboxamide];

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N-2-(4-Piperidinyl)ethyl-N'-(2-carboxyethyl)-2-methyl-1,3-benzene-dicarboxamide;

5 3-[(4-Piperidinyl)methoxy]-N-(2-carboxyethyl)phenylacetamide;

4-(Piperidin-4-yl)phenyl-3-propionyl-[2(S)-n-butylsulfonylamino]- β -alanine;

10 4-[(1,2,5,6-Tetrahydropyridin-4-yl)phenyl-3-propionyl-[2(S)-n-butylsulfonylamino]- β -alanine;

3-[3-(Piperidin-4-ylmethyl)phenyl]propionyl- β -alanine;

15 3-[4-(1,2,5,6-Tetrahydropyridin-4-yl)butyryl]- β -alanine;

{N-2-(4-Piperidinylethyl)-N'-3-[2(S)-n-butylsulfonylaminopropanoic acid]}-1,3-benzenedicarboxamide;

20 N-2-(4-Piperidinyl)ethyl-N'-3-[2(S)-n-butylsulfonylaminopropionic acid]-2-methyl-1,3-benzenedicarboxamide;

{N-[2-(4-Piperidinyl)ethyl]-N-(phenethyl)}-N'-(2-carboxyethyl)-1,3-benzenedicarboxamide;

25 N-[2-(4-Piperidinyl)ethyl-N-propyl]-N'-(2-carboxyethyl)-1,3-benzenedicarboxamide;

30 N-2-(4-Piperidinyl)ethyl-N'-[3-(2(S)-hexanoylaminopropionic acid)]-1,3-benzenedicarboxamide;

[N-2-(4-Piperidinyl)ethyl]-N'-[3-2(S)-thien-2-yl-sulfonylamino-propionic acid]-1,3-benzenedicarboxamide;

- 20 -

4-methyl-N-[2-(4-piperidinyl)ethyl]-N'-2-(carboxyethyl)-1,3-benzene-dicarboxamide;

5 3-[(2-Carboxyethyl)aminosulfonyl]-N-[2-(4-piperidinylethyl)]-benzamide;

3-[2-(4-Piperidinyl)ethylaminosulfonyl]-N-[(2-carboxyethyl)]-benzamide;

10 3-[(4-Piperidinyl)methylaminosulfonyl]-N-[(2-carboxyethyl)]-benzamide;

15 N-[(2-(N-BOC-4-Piperidinyl)ethyl)-N'-[(2-carboxyethyl)-3,5-pyridinedicarboxamide;

N-[2-(4-Piperidinyl)ethyl]-N'-[(2-carboxy)ethyl]-2,6-pyridinedicarboxamide;

20 3-(3-Carboxypropyloxy)-N-(4-piperidinylmethyl)carboxamide;

N-2-(4-Piperidinylethyl)-N'-3-(2-benzylpropionic acid)-1,3-benzenedicarboxamide;

25 3-(5-Carboxypentanoyl)-N-(4-piperidinylmethyl)benzenecarboxamide;

3-(6-Carboxyhexanoyl)-N-(4-piperidinylmethyl)benzenecarboxamide;

4-(Piperidin-4-yl)phenyl-3-propionyl- β -alanine;

30 4-(1,2,5,6-Tetrahydropyridin-4-yl)phenyl-3-propionyl- β -alanine;

6-[2-(Piperidin-4-yl)ethyloxy]nicotinamide-N-[3-(2(S)-phenylsulfonyl-amino)propionic acid;

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3-Chloro-4-[2-(Piperidin-4-yl)ethyloxy]phenylcarbonyl-2(S)-phenyl-sulfonylamino- β -alanine;

5 4-[3-(Piperidin-3-yl)propyloxy]-N-[3-(2(S)-butylsulfonylamino)-propionic acid]benzamide;

4-[2-(Piperidin-4-yl)ethyloxy]phenylcarboxyl-2-(S)-hydroxy- β -alanine.

10 N-[3-(2(S)-Phenylsulfonylamino)propionate]-4'-aminomethyl-4-biphenylcarboxamide;

N-[3-(2(S)-Phenylsulfonylamino)propionate]-4'-amidino-4-biphenylcarboxamide;

15 4-[3-(Pyridin-4-yl)propyloxy]benzoyl-2(S)-phenylsulfonylamino- β -alanine;

4-[3-(Pyridin-4-yl)propyl]benzoyl-2(S)-phenylsulfonylamino- β -alanine;

20 4-[2-(Piperidin-4-yl)oxyethyloxy]benzoyl-2(S)-phenylsulfonylamino- β -alanine;

4-N-(Piperazinyl)benzoyl-2(S)-phenylsulfonylamino- β -alanine;

25 4-[2-(N,N-Diethylamino)ethyloxy]benzoyl-2(S)-phenylsulfonylamino- β -alanine;

4-[4-(N-Morpholino)butyloxy]benzoyl-2(S)-phenylsulfonylamino- β -alanine;

30 4-[2-(N-Benzylimidazol-4-yl)ethyloxy]benzoyl-2(S)-phenylsulfonylamino- β -alanine;

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4-[2-(Imidazol-4-yl)ethyloxy]benzoyl-2(S)-phenylsulfonylamino- β -alanine;

5 4-[3-(1-Methylimidazol-4-yl)propyloxy]benzoyl-2(S)-phenylsulfonylamino- β -alanine methyl ester;

4-[3-(1-Methylimidazol-4-yl)propyloxy]benzoyl-2(S)-phenylsulfonylamino- β -alanine;

10 4-[3-(1-Imidazolyl)propyloxy]benzoyl-2(S)-phenylsulfonylamino- β -alanine t-butyl ester;

15 4-[3-(1-Imidazolyl)propyloxy]benzoyl-2(S)-phenylsulfonylamino- β -alanine;

4-[2-(Pyrrolidinyl)ethyloxy]benzoyl-2(S)-phenylsulfonylamino- β -alanine;

20 2(S)-Phenylsulfonylamino-4-(4-piperazinylphenoxy)butanoic acid;

t-Butyl 2(S)-t-Butyloxycarbonylamino-4-[4-N-methylpiperazinyl]phenoxy]butanoate;

25 2(S)-Amino-3-[4-(N-methylpiperazinyl)phenoxy]butanoic acid;

2(S)-3-Pyridylsulfonylamino-4-[4-(N-methylpiperazinyl)phenoxy]butanoic acid;

30 4-[(4-Pyrrolidinylbut-2-enyl)oxy]benzoyl-2(S)-phenylsulfonylamino- β -alanine t-butyl ester;

4-[(4-Pyrrolidinylbut-2-enyl)oxy]benzoyl-2(S)-phenylsulfonylamino- β -alanine;

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3-[(N-Boc-Piperidin-4-ylmethyl)aminocarbonyl]benzoyl-2(S)-3-pyridylsulfonylamino- β -alanyl-glycine benzyl ester;

5 3-[(Piperidin-4-ylmethyl)aminocarbonyl]benzoyl-2(S)-3-pyridylsulfonylamino- β -alanyl-glycine;

4-[(2-Aminoethyl)aminocarbonyl]benzoyl-2-(S)-phenylsulfonylamino- β -alanine;

10 4-[(2-Guanidinoethyl)aminocarbonyl]benzoyl-2(S)-phenylsulfonylamino- β -alanine;

4-[(4-N-Methylaminobutyl)aminocarbonyl]benzoyl-2(S)-3-pyridylsulfonylamino- β -alanine;

15

{N-2-(4-Piperidinylethyl)-N'-3-[ethyl 2(S)-n-butylsulfonylamino-propanoate]}-1,3-benzenedicarboxamide;

20

4-[2-(4-Piperidinyl)ethyloxy]-N-[3-(2(S)-n-butylsulfonylamino)-propionate]benzamide;

4-[2-(4-Piperidinyl)ethyloxy]-N-[3-(2(S)-n-phenylsulfonylamino)-propionate]benzamide;

25

3-[3-(Piperidin-4-ylmethyl)phenyl]propionyl- β -alanine; and

3-[(4-Piperidinyl)methyloxy]-N-[3-(2-indol-3-yl)ethyl-propionic acid]phenyl acetamide.

30

Platelet aggregation is measured at 37°C in a Chronolog aggregometer. The reaction mixture contains gel-filtered human platelets (2×10^8 per ml), fibrinogen (100 micrograms per ml (ug/ml)), Ca^{2+} (1mM), and the compound to be tested. The aggregation is initiated by adding 10 μM ADP 1 minute after the other components are

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added. The reaction is then allowed to proceed for at least 2 minutes. The extent of inhibition of aggregation is expressed as the percentage of the rate of aggregation observed in the absence of inhibitor. The IC₅₀ is the dose of a particular compound inhibiting aggregation by 50% relative to a control lacking the compound.

Activities of some of the preferred compounds, characterized by IC₅₀ for inhibition of ADP-mediated platelet aggregation, are listed below:

| | IC ₅₀ |
|--|------------------|
| 3-[4-(1,2,5,6-Tetrahydropyridine)-phenyl]butyryl-β-alanine | 1.3 μM |
| 3-[3-Piperidin-4-ylmethyl]phenyl]-propionyl-β-alanine; | 170 μM |
| 3-[4-Piperidinyl)methoxy]-N-[3-(2-indol-3-yl)ethylpropionic acid]phenyl-acetamide; | 5.2 μM |
| 3-[(4-Piperidinyl)methoxy]-N-(2-carboxyethyl)-phenyl acetamide; | 56 μM |
| 4-(4-Piperidin-4-yl)-N-3[2(S)-n-butylsulfonylamino]propionic acid]-phenylbutyramide; | 0.095 μM |
| 4-[2-Piperidin-4-yl)ethoxy]benzoyl-2(S)-phenylsulfonylamino-β-alanine; | 0.014 μM |
| 4-(Piperidin-4-yl)phenyl-3-propionyl-[2(S)-n-butyl-sulfonylamino]-β-alanine; | 0.10 μM |

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| | | |
|----|--|---------------|
| 5 | 3-[4-(1,2,5,6-Tetrahydropyridin-4-yl)-phenyl]butyryl- β -alanine; | 1.3 μ M |
| | 4-(1,2,5,6-Tetrahydropyridin-4-yl)-phenyl-3-propionyl-[2(S)-butylsulfonylamino]- β -alanine; | 0.022 μ M |
| 10 | 4-(Piperidin-4-yl)-phenyl-3-propionyl- β -alanine; | 11 μ M |
| 15 | 4-(1,2,5,6-Tetrahydropyridin-4-yl)-phenyl-3-propionyl- β -alanine; | 1.7 μ M |

The novel compounds of the present invention were prepared according to the procedure of the following examples. The most preferred compounds of the invention are any or all of those specifically set forth in these examples. These compounds are not, however, to be construed as forming the only genus that is considered as the invention, and any combination of the compounds or their moieties may itself form a genus. The following examples further illustrate details for the preparation of the compounds of the present invention. Those skilled in the art will readily understand that known variations of the conditions and processes of the following preparative procedures can be used to prepare these compounds. All temperatures are degrees Celsius unless otherwise noted.

Compounds of the present invention are prepared from dicarboxylic acids by a sequence of carboxyl activation with CDI or other suitable reagent, followed by amide bond formation. In this manner, representative compounds of Schemes 1, 2, 3 and 7 may be prepared using amines that have been previously protected as esters or carbamates. Subsequent to coupling with, for example, a CBZ-protected amine, the product may be deprotected at a N site and

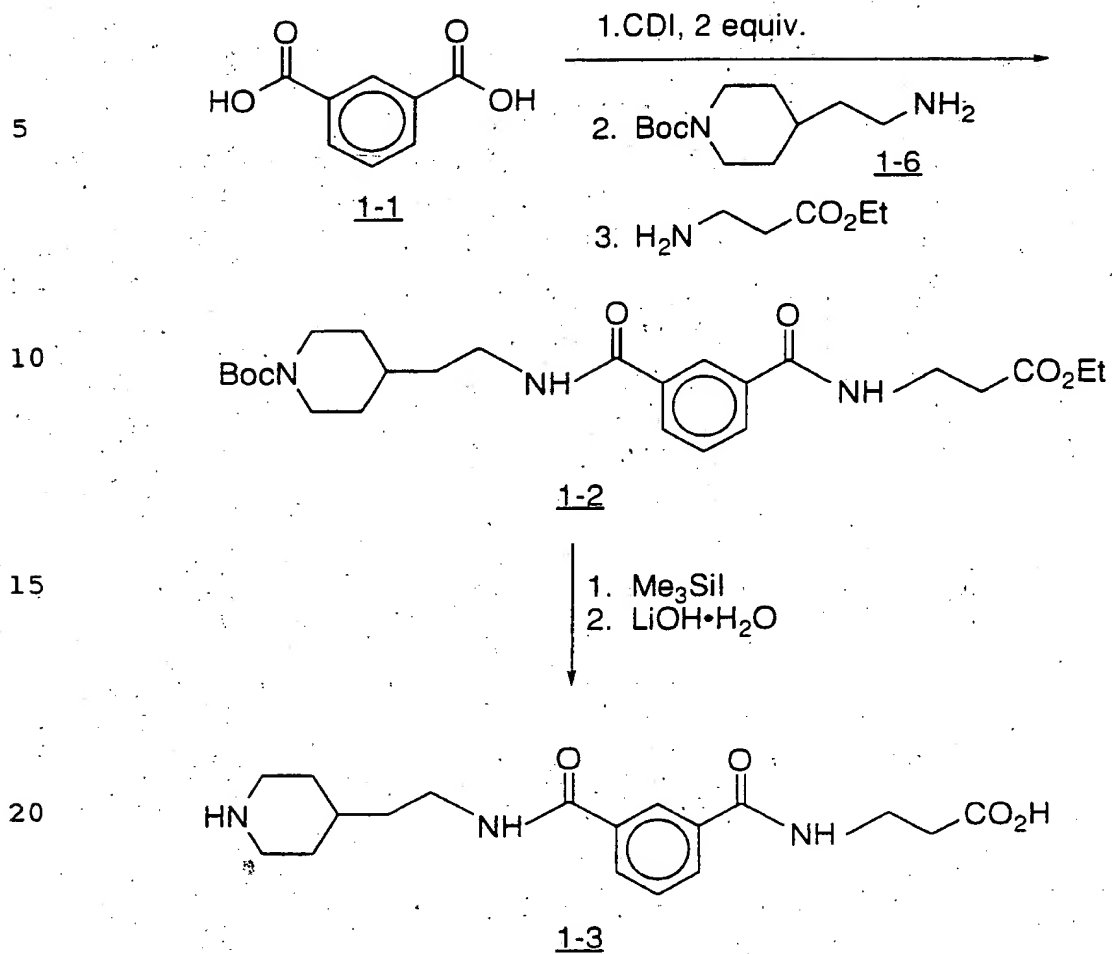
functionalized to a sulfonamide or amide via sulfonylating or acylating reagents, respectively.

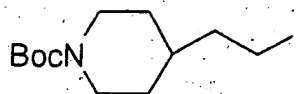
Differentially functionalized chlorosulfonyl benzoic acids, as shown in Schemes 3 and 4, may be prepared from the corresponding sulfonic acid and, via treatment with appropriate amines, provide functionalized aryl sulfonamides. Subsequent activation of carboxyl groups followed by amide bond formation may provide further examples of desired compounds.

Ether analogs, such as shown in Schemes 9 and 13 may be prepared by treatment of the appropriate hydroxy carboxylic acid with a base, such as NaH, to form the alkoxide followed by reaction with an alkylating agent. This alkylating agent may encompass suitably protected amine components. Subsequent to alkylation, carboxyl activation and amide formation may provide advanced synthetic intermediates. Deprotection as appropriate may then provide key products of the present invention.

In addition to the following preparative procedures, several examples of in-vitro bioactivity of compounds within the scope of the present invention are indicated. To illustrate, one test which is used to evaluate fibrinogen receptor antagonist activity is based on evaluation of inhibition of ADP-stimulated platelets. Aggregation requires that fibrinogen bind to and occupy the platelet fibrinogen receptor site. Inhibitors of fibrinogen binding inhibit aggregation. In the ADP-stimulated platelet aggregation assay used to determine inhibition associated with the compounds claimed in the instant invention, human platelets are isolated from fresh blood, collected into acid citrate/dextrose by differential centrifugation followed by gel filtration on Sepharose 2B in divalent ion-free Tyrode's buffer (pH 7.4) containing 2% bovine serum albumin.

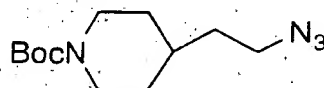
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SCHEME 1



5 2-(N-Boc-4-Piperidinyl)ethyl iodide (1-4)

10 1-4 is prepared according to the procedure described in European Publication 540,334, specifically at pages 17-18 and 21 of that publication, for preparing compound 1-6 of EP 540,334. Boc-4-piperidine-2-ethanol (10.42g, 0.048 moles) was dissolved in benzene (400 ml), and imidazole (4.66g, 0.068 moles) and triphenylphosphine (13.24g, 0.05 moles) were added at room temp, followed by iodine (12.9 g, 0.05 mol). After 6 hours the reaction mixture was filtered and the filtrate was evaporated to give a dark residue. This was purified by
15 flash chromatography on silica gel eluting with 10% EtOAc/hexanes to give 1-4 as a yellow oil. R_f 0.3 (silica, 10% EtOAc/hexanes).



20 2-(N-Boc-4-Piperidinyl)ethyl azide (1-5)

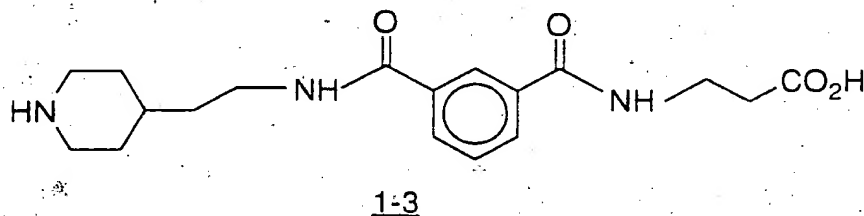
25 To 1-4 (27.9g, 0.082 moles) dissolved in DMSO (400 ml) was added sodium azide (5.61g, 0.086 moles) at room temperature and the resulting solution was heated at 65° for 2 hrs. The cooled reaction mixture was diluted with 250 ml EtOAc, extracted with 2x100 ml portions of water, 2x50 ml portions of brine and then dried (MgSO₄). Solvent removal provided 1-5 as a pale yellow oil, R_f 0.5 (silica gel,
30 20% acetone/hexane).



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2-(N-Boc-4-Piperidinyl)ethyl amine (1-6)

To a solution of 1-5 (19.3g, 0.076 moles) in THF (400 ml)/H₂O (195 ml) was added triphenylphosphine (80.0g, 0.305 moles) in one portion at room temperature. This was stirred for 3 hours and the solvent was then removed in vacuo. The residue was acidified to pH 2 with 10% KHSO₄ solution and this was extracted with 4x100 ml portions of EtOAc. The organic extract was extracted with 2x100 ml portions of 10% KHSO₄ and the aqueous phases were combined and the pH was adjusted to pH 10 with 2N NaOH. This solution was extracted with EtOAc and the organic phase was dried (MgSO₄), and the solvent was removed to give 1-6 as a yellow liquid, R_f 0.3 (silica gel 10% CH₃OH in CHCl₃/NH₃),
¹H NMR (300 MHz, CDCl₃) δ 4.05 (broad, 2H), 2.72 (t, J=7.2Hz, 2H), 2.62 (m, 2H), 1.64 (d, J=12.2Hz, 2H), 1.43 (s, 9H), 1.42-1.32 (m, 5H), 1.09 (m, 2H).

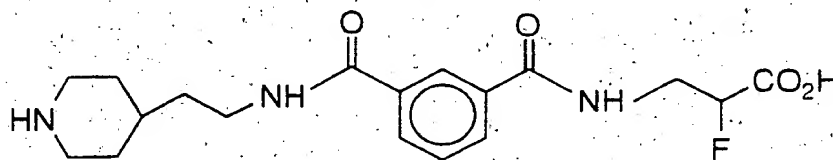
[N-2-(4-Piperidinyloethyl)-N'-(2-carboxyethyl)]-1,3-benzenedicarboxamide (1-3)

To 1,3-benzenedicarboxylic acid (Aldrich) (0.36g, 0.22 mmoles) in 3 ml DMF was added carbonyldiimidazole (CDI) (0.71g, 0.44 mmoles) in small portions as the reaction mixture vigorously evolved gas. After stirring at room temperature for 0.5 hr 1-6 (0.5g, 0.22 mmoles) in 2 ml DMF was added and the resulting solution was stirred for 1.2 hours. Then, N-methyl-morpholine (NMM) (0.72 ml, 0.66 mmoles) was added followed by β-alanine ethyl ester (0.33g, 0.22 mmoles) and the resulting mixture was stirred at room temperature for 6 hours.

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The solvent was removed and the residue was taken up in H₂O, acidified with 10% aqueous KHSO₄ solution, and this was extracted with EtOAc. The extracts were dried (MgSO₄), and the solvent was removed to afford a residue that was purified by flash chromatography on silica gel eluting with 3% methanol/CH₂Cl₂ to give [N-Boc-2-(4-piperidinyethylamino)-N'-(2-carboethoxyethylamino)-1,3-benzenedicarboxamide (1-2), R_f 0.3 (silica gel, 5% MeOH/CH₂Cl₂). ¹H NMR (300 MHz, CDCl₃) δ 8.18 (s, 1H), 7.93 (d, J=7.8Hz, 1H), 7.86 (d, J=7.8Hz, 1H), 7.46 (t, J=7.8Hz, 1H), 7.22 (t, J=5.7Hz, 1H), 6.77 (t, J=5.4Hz, 1H), 4.15 (q, J=7.1Hz, 2H), 4.05 (d, J=13.2Hz, 2H), 3.70 (dd, J=6.1, 12.0Hz, 2H), 3.46 (dd, J=6.7, 13.1Hz, 2H), 2.63 (t, J=6.1Hz, 2H), 2.6 (m, 2H), 1.67 (d, J=11.2Hz, 2H), 1.54 (m, 2H), 1.45 (s, 9H), 1.26 (t, J=7.1Hz, 3H), 1.1 (m, 2H).

Ester 1-2 (0.27g) was dissolved in CH₂Cl₂ (10 ml) and at room temperature trimethylsilyliodide (TMSI) (0.071 mmoles) was added and after 10 minutes stirring starting material was consumed. MeOH (2 ml) was added to quench the reaction and the solvent was removed in vacuo. The residue was dissolved in 1:1:1 THF/MeOH/H₂O (10 ml), lithium hydroxide (0.24g, 5.68 mmoles) was added, and the reaction mixture was stirred at room temperature. After 1.0 hour the solvent was removed and the residue purified by flash chromatography on silica gel eluting with 9:1:1 EtOH/H₂O/NH₄OH to give 1-3 (R_f 0.3, silica gel, 9:1:1 EtOH/H₂O/NH₄OH, ninhydrin stain). ¹H NMR (300 MHz, CD₃OD) δ 8.22 (s, 1H), 7.95 (m, 2H), 7.54 (m, 1H), 3.60 (s, 2H), 3.4 (m, 6H), 2.90 (m, 2H), 2.47 (s, 2H), 2.0 (s, 2H), 1.8-1.6 (m, 3H), 1.5-1.4 (m, 2H). Mass spectrum (FAB) 348 (M+1).



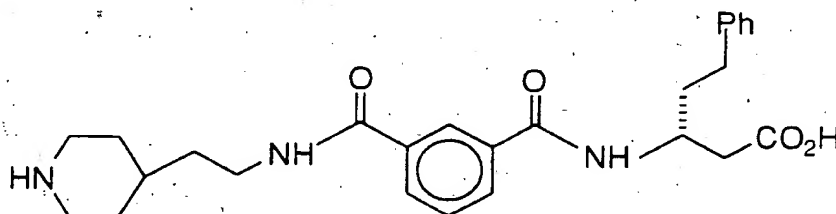
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[N-2-(4-Piperidinyloethyl)-N'-[3-(2-fluoro)propanoic acid]-1,3-benzenedicarboxamide (1-7)]

This was prepared as described for 1-3, wherein 2-fluoro- β -alanine ethyl ester (American Tokyo Kasai) was used as the C-terminal amino acid component.

¹H NMR (300 MHz, CD₃OD) δ 8.25 (s, 1H), 7.96 (d, 7.1Hz, 2H), 7.56 (t, J=7.7Hz, 1H), 5.0 (m, 1H), 4.0-3.85 (m, 2H), 3.45 (t, J=6.7 Hz, 2H), 3.32 (d, J=11.7Hz, 2H), 2.98 (dt, J=2.8, 12.9Hz, 2H), 2.00 (d, J=14.6Hz, 2H), 1.75 (m, 1H), 1.65 (dd, J=6.8, 13.4Hz, 2H), 1.45 (m, 2H)

Mass spectrum (FAB) 366 (M+1).



1-8

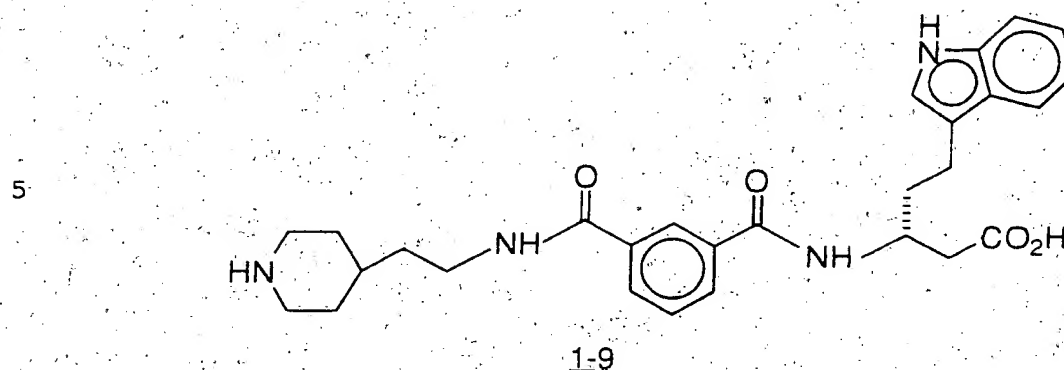
{N-2-(4-Piperidinyloethyl)-N'-3-[3(R)-phenethyl-propanoic acid]}-1,3-benzenedicarboxamide (1-8)

This was prepared as described for 1-3 but using 3-R-phenethyl- β -alanine ethyl ester (the TFA salt of which is prepared according to the procedure of Example 15, page 36, of European Publication 478362) as the C-terminal amino acid component 1-10 had R_f 0.3 (silica gel, 9:1:1 EtOH/H₂O/NH₄OH, ninhydrin stain).

¹H NMR (300 MHz, CD₃OD) δ 8.20 (d, J=1.5Hz, 1H), 7.97 (m, 2H), 7.56 (t, J=7.75Hz, 1H), 7.20 (m, 4H), 7.12 (m, 1H), 4.43 (t, J=6.7Hz, 1H), 3.45 (t, J=6.5Hz, 2H), 3.32 (m, 2H), 2.97 (t, J=12.6Hz, 2H), 2.71 (t, J=8.0Hz, 2H), 2.51 (d, J=5.7Hz, 2H), 1.98 (m, 4H), 1.70 (m, 1H), 1.65 (m, 2H), 1.50 (m, 2H)

Mass spectrum (FAB) 452 (M+1)

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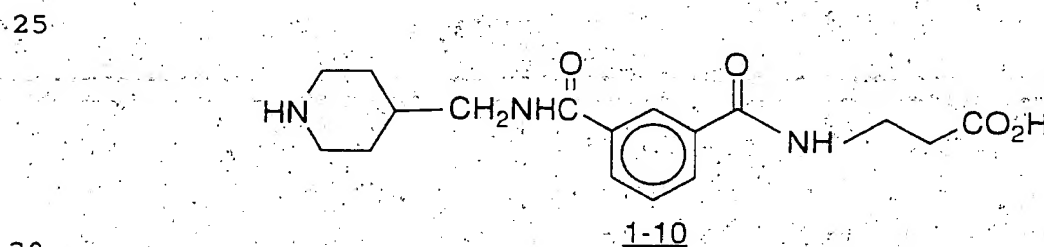


{N-[2-(4-Piperidylethyl)-N'-3-[3(R)-indolylethyl-propanoic acid]]-
1,3-benzenedicarboxamide (1-9)

This was prepared as described for 1-3 but using 3-R-
 (indol-3-ylethyl)- β -alanine ethyl ester (the preparation of which is
 identified therein as compound 7a) as the C-terminal amino acid
 component.

¹H NMR (300 MHz, CD₃OD) δ 8.20 (d, J=1.6Hz, 1H), 7.95 (m, 2H),
 7.53 (m, 2H), 7.27 (d, J=8.1Hz, 1H), 7.05-6.90 (m, 3H), 4.50 (t,
 J=6.2Hz, 1H), 3.43 (t, J=6.7Hz, 2H), 3.30 (m, 2H), 2.90 (m, 4H), 2.54
 (d, J=5.9Hz, 2H), 2.10 (dd, J=7.0, 15.5Hz, 2H), 1.91 (d, J=15.0Hz, 2H),
 1.6 (m, 3H), 1.4 (m, 2H)

Mass spectrum (FAB) 491 (M+1)

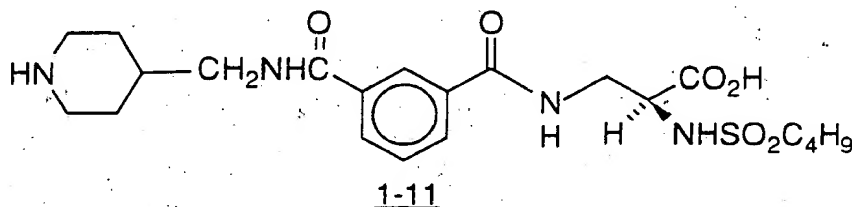


N-(4-Piperidinylmethyl)-N'-(2-carboxyethyl)-1,3-benzenedi-
 carboxamide (1-10)

- 33 -

Treatment of 1-1 with 6-2 and β -alanine ethyl ester as described for 1-2, followed by hydrolysis ($\text{LiOH}\cdot\text{H}_2\text{O}$) and deprotection (HCl gas) as described for 3-4 provided pure 1-10.

^1H NMR (300 MHz, CD_3OD) δ 0.55 (2H, m), 0.92 (3H, bd), 1.44 (2H, t), 1.92 (2H, t), 2.35 (4H, m), 2.56 (2H, t), 6.50 (1H, t), 6.88 (2H, dt), 7.15 (1H, s).

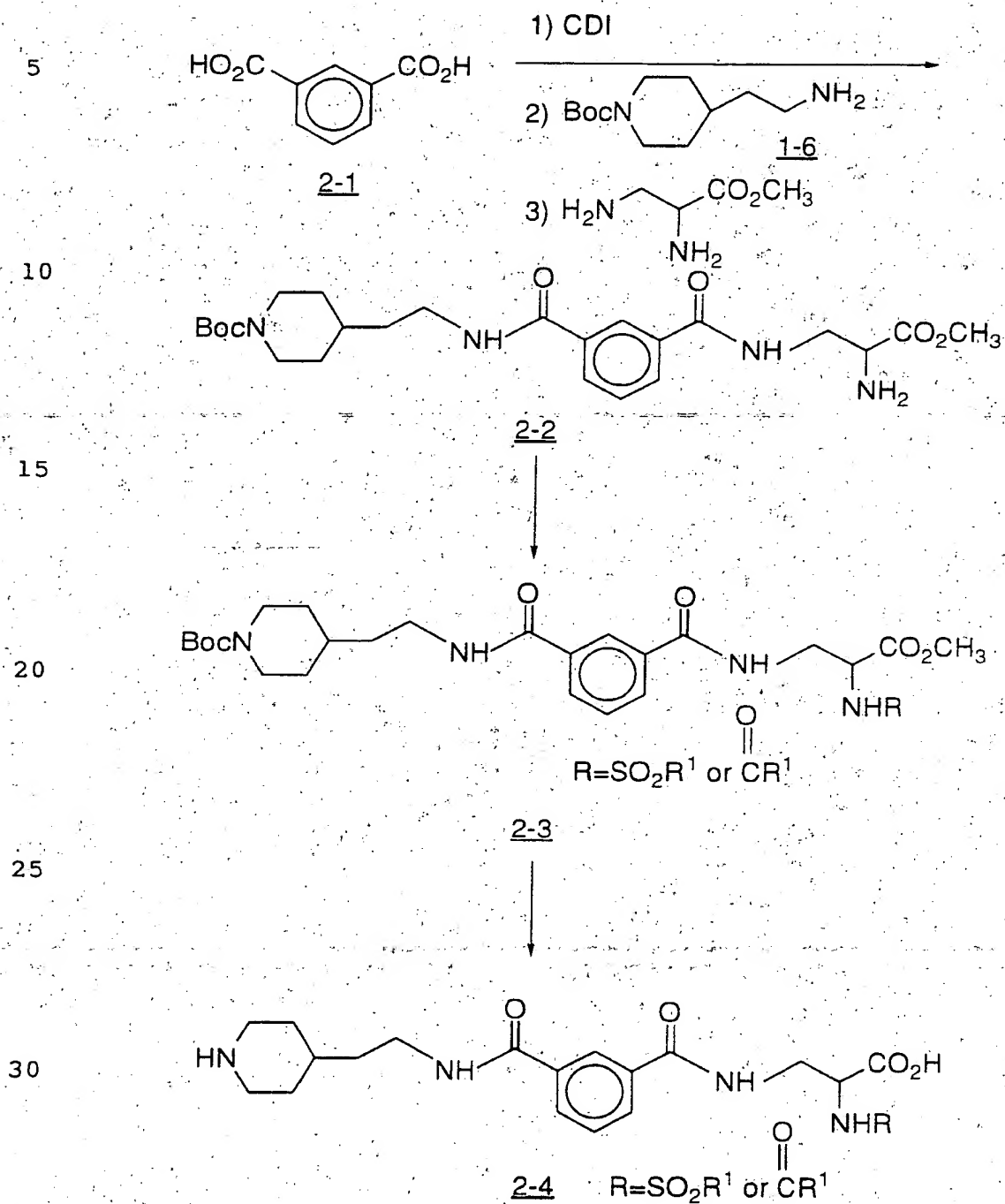


N-(4-Piperidinylmethyl)-N'-[3-(2(S)-n-butylsulfonyl-aminopropionic acid)-1,3-benzenedicarboxamide (1-11)]

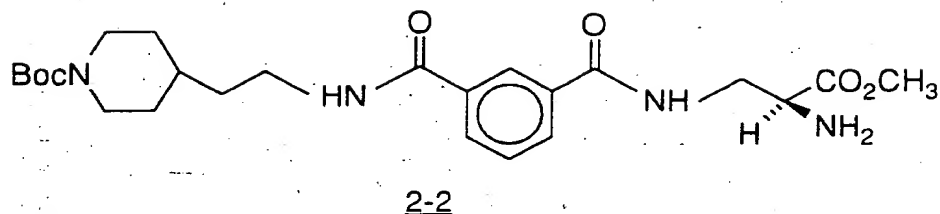
Treatment of 1-1 with 6-2 and 9-3 as described for 1-2, followed by hydrolysis ($\text{LiOH}\cdot\text{H}_2\text{O}$) and deprotection (HCl gas) as described for 3-4 gave pure 1-11, R_f 0.25 (silica, $\text{EtOH}/\text{NH}_4\text{OH}/\text{H}_2\text{O}$ (10:1:1)).

^1H NMR (300 MHz, CD_3OD) δ 0.63 (3H, t), 1.15 (2H, m), 1.36 (2H, m), 1.54 (2H, m), 1.90 (2H, bd), 2.87 (2H, dt), 2.98 (2H, t), 3.25 (2H, d), 3.28-3.45 (3H, m), 3.69 (1H, dd), 3.92 (1H, dd), 7.50 (1H, t), 7.82 (2H, t), 7.98 (1H, s).

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SCHEME 2

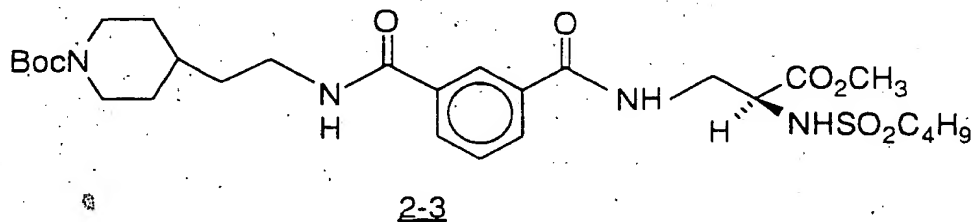
- 35 -



10 {N-2-(N'-Boc-4-Piperidinylethyl)-N''-3-[methyl 2(S)-amino-
propanoate] }-1,3-benzenedicarboxamide (2-2)

To a solution of 1,3-benzenedicarboxylic acid (0.27 g, 1.66 mmol) in 10 ml DMF was added carbonyl diimidazole (CDI) (0.54 g, 3.32 mmol) at 0° and this was stirred for 1.0 hour. Then, 1-6 (0.38 g, 1.66 mmol) was added and the resulting solution was stirred for 4.0 hrs. Methyl 2(S),3-diaminopropanoate (9-8) (0.315 g, 1.66 mmol) and N-methylmorpholine (NMM) (4.98 mmol) were added and the resulting solution was stirred for 16 hours. The solvent was removed and the residue was dissolved in H₂O, acidified with 10% KHSO₄ solution and extracted with EtOAc. The aqueous phase was adjusted to pH 10 and extracted with EtOAc. Solvent removal provided 2-2 as a gum (0.45 g).

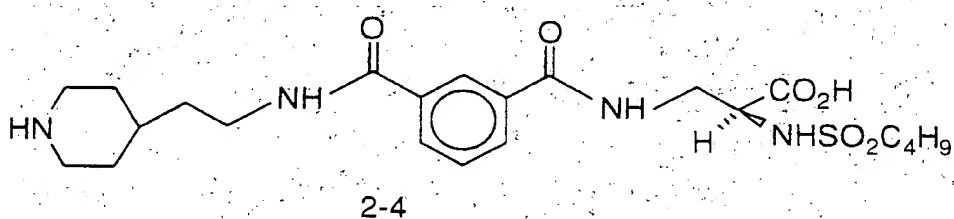
¹H NMR (300 MHz, CDCl₃) δ 8.5 (broad, 2H), 8.28 (s, 1H), 7.92 (m, 2H), 7.54 (m, 1H), 7.44 (t, J=7.7 Hz, 1H), 4.0 (m, 2H), 3.8-3.6 (m, 1H), 3.68 (s, 3H), 3.50 (m, 1H), 3.40 (m, 2H), 2.60 (m, 2H), 1.6 (d, J=12.7 Hz, 2H), 1.5-1.4 (m, 3H), 1.41 (s, 9H), 1.05 (m, 2H).



{N-2-(N'-Boc-4-Piperidinyloethyl)-N''-3-[methyl 2(S)-n-butylsulfonyl-aminopropanoate] }-1,3-benzenedicarboxamide (2-3)

To 2-2 (0.45 g, 0.95 mmoles) in CH₂Cl₂ (10 ml) at room temperature was added pyridine (5 mmoles) followed by n-butanesulfonyl chloride (5 mmoles). The reaction mixture was heated at reflux for 8 hours and the solvent was removed. The residue was dissolved in CHCl₃, washed with 10% KHSO₄ solution, brine, dried (Na₂SO₄) and the solvent removed. The resulting residue was purified by flash chromatography on silica gel eluting with 5% MeOH/CHCl₃ to give 2-3.

¹H NMR (300 MHz, CDCl₃) δ 8.10 (s, 1H), 7.86 (t, J=8.1 Hz, 2H), 7.66 (t, J=5.9Hz, 1H), 7.38 (t, J=7.7Hz, 1H), 6.84 (t, J=5.5 Hz, 1H), 4.42 (d, J=9.0 Hz, 1H) 4.37 (m, 1H), 4.02 (d, J=12.5 Hz, 2H), 3.95 (m, 1H), 3.76 (s, 3H), 3.70 (m, 1H), 3.25 (m, 2H), 3.00 (t, J=7.9 Hz, 2H); 2.66 (t, J=12.1 Hz, 2H), 1.70 (m, 2H), 1.60 (d, J=13.6 Hz, 2H) 1.43 (s, 9H), 1.40-1.30 (m, 5H), 1.06 (m, 2H), 0.86 (t, J=7.3 Hz, 3H).



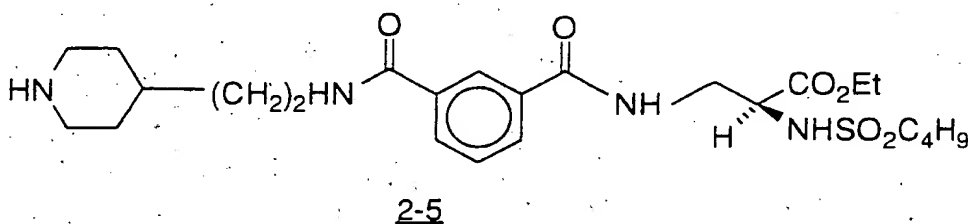
{N-2-(4-Piperidinyloethyl)-N'-3-[2(S)-n-butylsulfonyl-aminopropanoic acid] }-1,3-benzenedicarboxamide (2-4)

To 2-3 (0.10g, 0.167 mmoles) in CH₂Cl₂ (10ml) at room temperature was added trimethylsilyl iodide (TMSI) (0.35 mmoles). The yellow solution was stirred for 15 min, and then MeOH (5ml) was added to quench the reaction. The solvent was removed and the residue was dissolved in THF(1)/H₂O(1)/MeOH(1) and lithium hydroxide monohydrate (0.070g, 1.67 mmoles) was added. After stirring for 1 hour the solvent was removed and the residue was purified by flash

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chromatography on silica gel eluting with EtOH(9)/H₂O(1)/NH₄OH(1) to give pure 2-4.

¹H NMR (300 MHz, D₂O) δ 8.21 (s, 1H), 8.01 (m, 2H), 7.75 (t, J=7.8 Hz, 1H), 3.91 (dd, J=5.1, 8.8 Hz, 1H), 3.78 (dd, J=5.1, 12.9 Hz, 1H), 3.51 (m, 3H), 3.03 (d, J=11.3 Hz, 2H), 2.94 (t, J=8.0 Hz, 2H), 2.55 (d, J=12.2 Hz, 2H), 1.80-1.55 (m, 7H), 1.40-1.20 (m, 4H), 0.87 (t, J=7.5 Hz, 3H).

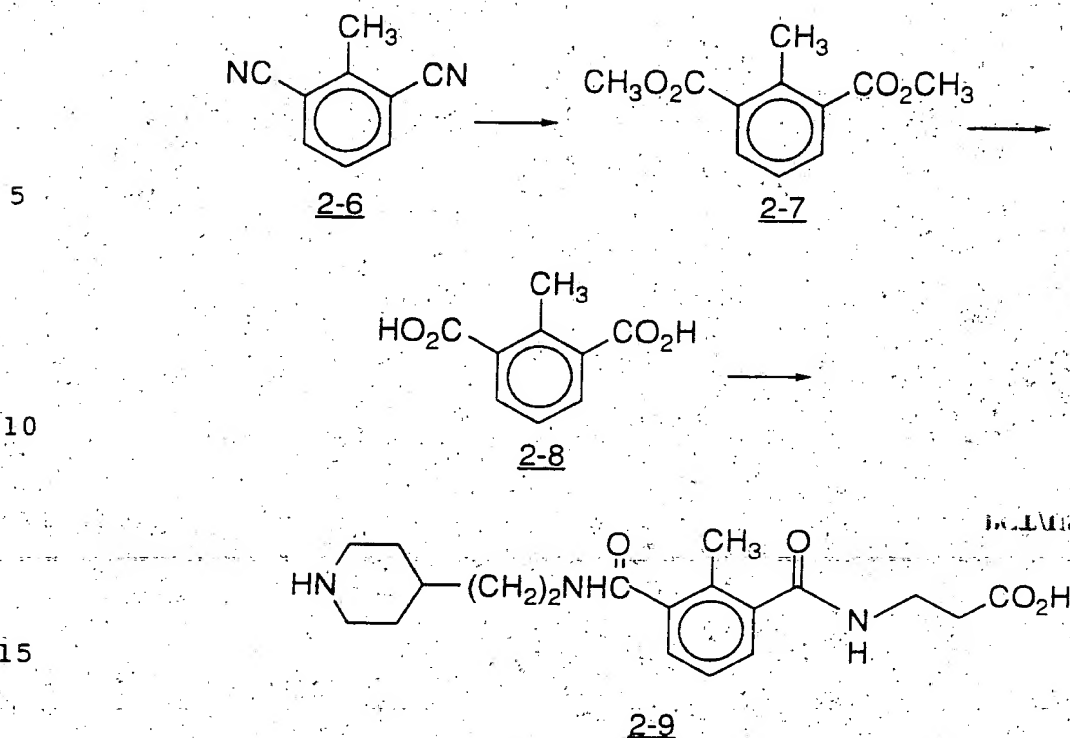


{N-2-(4-Piperidylethyl)-N'-3-[ethyl 2(S)-n-butyl-sulfonylamino-propanoate]}-1,3-benzenedicarboxamide (2-5)

Treatment of 2-3, with HCl gas in EtOAc, as described for 2-4, gave 2-5 as a white solid.

¹H NMR (300 MHz, CD₃OD) δ 0.90 (3H, t), 1.30 (3H, t), 1.4-1.5 (4H, m), 1.6-1.8^{*} (5H, m), 2.05 (2H, d), 3.0 (4H, m), 3.39 (2H, d), 3.45 (2H, m), 3.61 (1H, dd), 3.80 (1H, dd), 4.23 (2H, q), 4.38 (1H, dd), 7.80 (2H, t), 8.0 (2H, d), 8.32 (1H, s).

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20 Dimethyl 2-methylbenzene-1,3-dicarboxylate (2-7)

A suspension of dicyano compound 2-6 (Aldrich) (10.0 g, 7.04 mmols) in H₂SO₄ (75% aqueous, 200 g) was heated at 160° for 4 hours. The cooled reaction mixture was added to H₂O and after settling overnight, the solid product was collected. The aqueous phase was extracted with EtOAc and this was concentrated and combined with the solid collected by filtration. This was dissolved in CH₃OH, treated with HCl gas at room temperature for 24 hours and concentrated. The residue was taken up in EtOAc, washed with saturated NaHCO₃, brine, dried (MgSO₄) concentrated and the residue purified by flash chromatography on silica gel eluting with 5% EtOAc/hexanes to give pure 2-7.

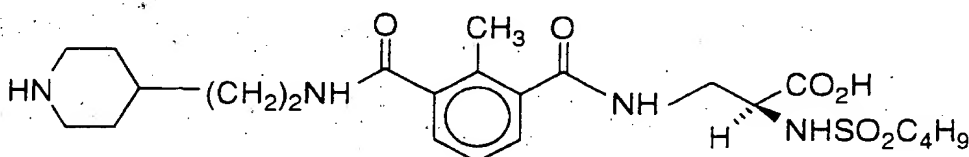
30 ¹H NMR (300 MHz, CDCl₃) δ 2.70 (3H, s), 3.92 (6H, s), 7.29 (1H, m), 7.88 (2H, m).

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[N-2-(4-Piperidiny)ethyl-N'-(2-carboxyethyl)]-2-methyl-1,3-benzene-dicarboxamide (2-9)

Diester 2-7 was treated with LiOH·H₂O in THF/MeOH/H₂O (1:1:1) as described for 3-4 to provide the desired diacid. This was treated with 1-6 and β-alanine ethyl ester as described for 2-2. Hydrolysis and deprotection with HCl gas in EtOAc as described for 3-4 provided 2-9 as a white solid.

¹H NMR (300 MHz, CD₃OD) δ 1.45 (2H, m), 1.63 (3H, m), 2.03 (2H, bd), 2.36 (3H, s), 2.64 (2H, t), 2.98 (2H, dt), 3.61 (2H, t), 7.35 (3H, m).



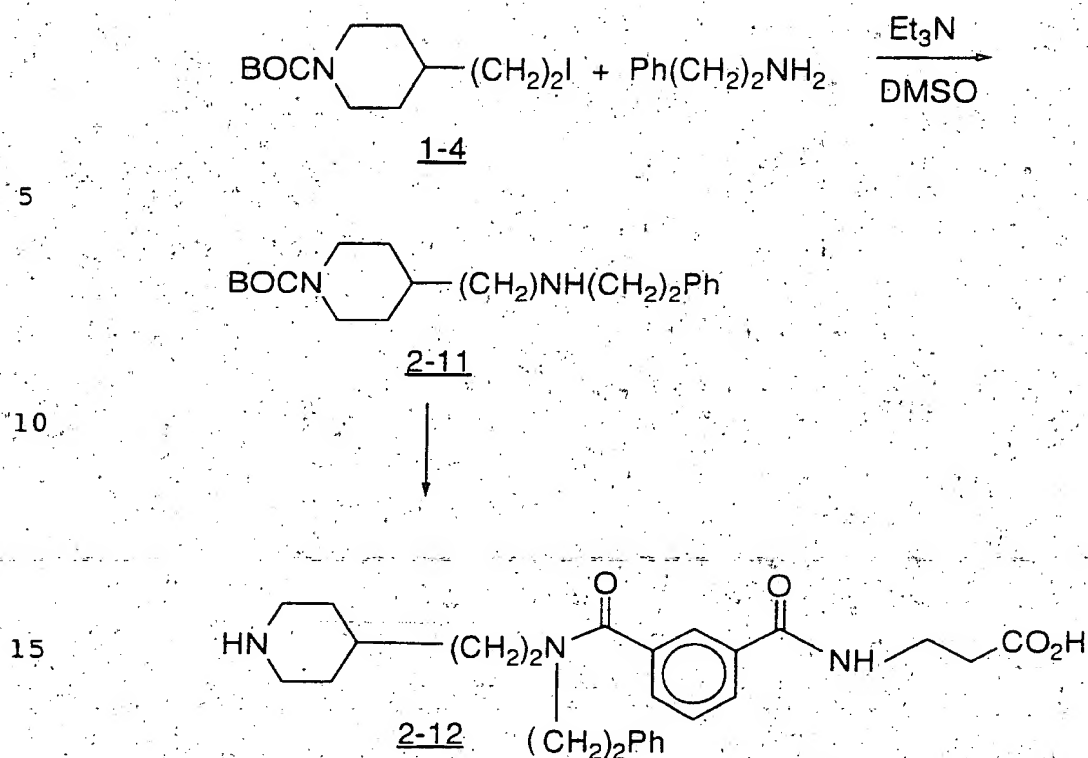
2-10

N-2-(4-Piperidiny)ethyl-N'-3-[2(S)-n-butylsulfonyl-aminopropionic acid]-2-methyl-1,3-benzenedicarbox-amide (2-10)

This compound was prepared in similar fashion to 2-9 wherein 9-3 was employed to provide 2-10.

¹H NMR (300 MHz, CD₃OD) δ 0.97 (3H, t), 1.45 (4H, m), 1.44 (2H, m), 1.74 (3H, m), 2.03 (2H, bd), 2.40 (3H, s), 2.99 (2H, dt), 3.10 (2H, t), 3.52 (1H, m), 3.84 (1H, dd), 4.33 (1H, m), 7.30 (1H, t), 7.38 (1H, m), 7.51 (1H, dd).

- 40 -



20 [N-2-(N'-BOC-4-Piperidiny]ethyl]phenethylamine (2-11)

A solution of phenethylamine (1.07 g, 8.83 mmoles) and Et₃N (1.78 g, 17.6 mmoles) in DMSO (25 ml) was cooled to 0° and treated with 1-4 and this was stirred for 4 hours. The reaction mixture was diluted with EtOAc, washed with saturated NaHCO₃, brine, dried (MgSO₄) and concentrated. The residue was purified by flash chromatography on silica gel eluting with 2% CH₃OH/CHCl₃(NH₃) to give pure 2-11.

¹H NMR (300 MHz, CDCl₃) δ 1.10 (2H, m), 1.44 (9H, s), 1.62 (3H, m), 2.67 (4H, m), 2.85 (4H, m), 4.04 (2H, b), 7.22 (2H, m), 7.40 (3H, m).

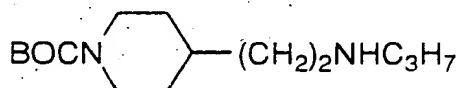
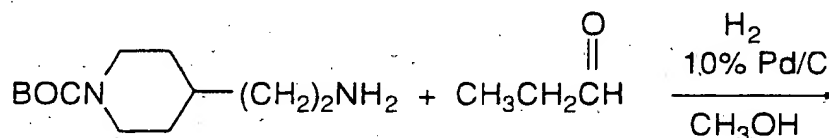
{N-[2-(4-Piperidiny]ethyl]-N-(phenethyl)}-N'-(2-carboxyethyl)-1,3-benzenedicarboxamide (2-12)

This compound was prepared in similar fashion to 2-9 wherein 2-11 and β-alanine ethyl ester were used as the amine

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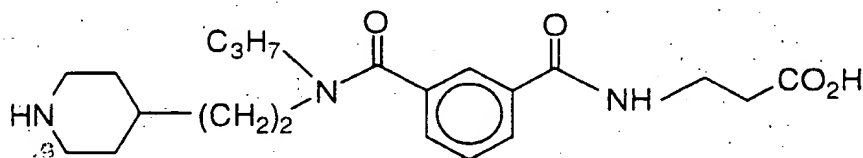
components. Hydrolysis ($\text{LiOH} \cdot \text{H}_2\text{O}$) and deprotection (HCl gas in EtOAc) as described for 3-4 provided 2-12 as a white solid.

^1H NMR (300 MHz, CD_3OD) δ 0.80 (2H, m), 1.00 (2H, m), 1.15 (1H, m), 2.13 (2H, m), 2.32 (2H, m), 2.62 (3H, m), 3.24 (2H, m), 3.35 (1H, m), 6.54 (1H, b), 6.82 (1H, b), 6.93 (2H, m), 7.05 (1H, bd), 7.19 (1H, bt), 7.45 (1H, bs), 7.57 (1H, bd).

2-13

[N-2-(N'-BOC-4-Piperidiny)ethyl]propylamine (2-13)

A solution of 2-(N-BOC-4-piperidiny)ethylamine (1-6) (1.0 g, 4.39 mmol) in CH_3OH (5 ml) was treated with propionaldehyde (4.50 mmol) and 10% Pd/C (0.25 g) and the resulting suspension was hydrogenated at 1 atmosphere for 20 hours. The catalyst was removed by filtration, the solution concentrated and the residue purified by flash chromatography on silica gel eluting with 2% $\text{CH}_3\text{OH}/\text{CHCl}_3(\text{NH}_3)$. R_f 0.4 (silica, 10% $\text{CH}_3\text{OH}/\text{CHCl}_3(\text{NH}_3)$).

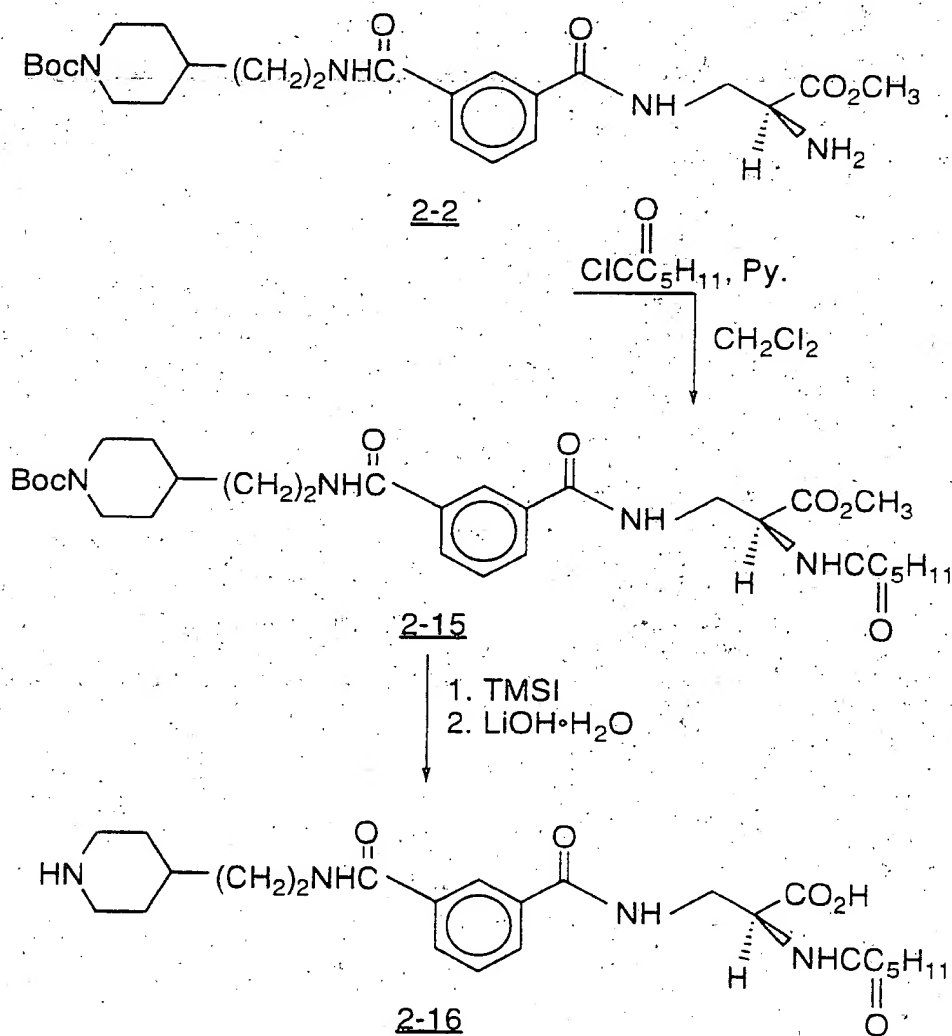
2-14

- 42 -

N-[2-(4-Piperidiny)ethyl-N-propyl]-N'-(2-carboxy-ethyl)-1,3-benzene-dicarboxamide (2-14)

This compound was prepared in similar fashion to 2-9 wherein 2-13 and β -alanine ethyl ester were used as the amine components. Hydrolysis ($\text{LiOH} \cdot \text{H}_2\text{O}$) and deprotection (HCl gas in EtOAc) as described for 3-4 gave 2-14.

^1H NMR (300 MHz, CD_3OD) δ 1.02 (3H, t), 1.28 (2H, m), 1.46 (3H, m), 1.68 (4H, m), 3.20 (4H, m), 3.48 (2H, t), 3.62 (4H, m), 7.52 (1H, d), 7.59 (1H, t), 7.88 (1H, bs), 7.98 (1H, d).



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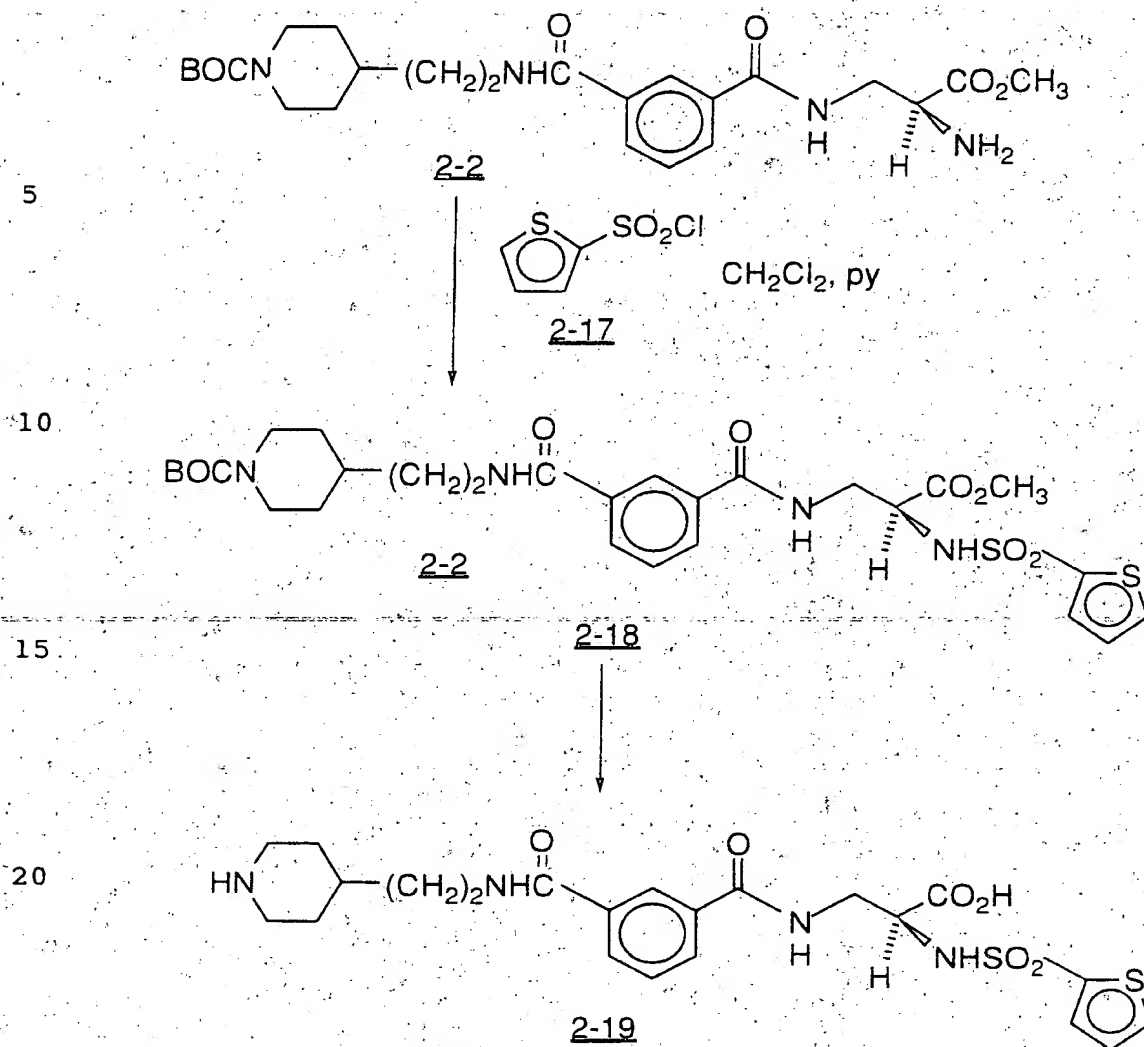
N-[2-(N'-Boc-4-Piperidiny)ethyl]-N''-[3-(methyl 2(S)-hexanoylamino-propionate)]-1,3-benzenedicarboxamide (2-15)

5 A solution of 2-2 (0.6 g, 1.26 mmoles) in CH₂Cl₂ (15 ml) was treated with pyridine (3.78 mmoles), cooled to 0°, and then treated with hexanoyl chloride (3.78 mmoles) and the solution was then stirred at ambient temperature for 4 hours. The solvent was removed, and the residue dissolved in 10% KHSO₄ solution to pH 2-3, extracted with CH₂Cl₂ and this was washed with brine, dried (MgSO₄) and
10 concentrated to give 2-15. R_f 0.65 (silica, 10% MeOH/CHCl₃(NH₃)).

N-2-(4-Piperidiny)ethyl-N'-[3-(2(S)-hexanoylamino-propionic acid)]-1,3-benzenedicarboxamide (2-16)

15 A solution of 2-15 (0.545 g, 0.95 mmoles) in CH₂Cl₂ (50 ml) was treated at room temperature with TMSI (2.9 mmoles) and after stirring for 15 minutes, the reaction was quenched with 20 ml CH₃OH. The solvent was removed and the residue was dissolved in THF/MeOH/H₂O (1:1:1) (45 ml) and treated with LiOH·H₂O (0.42 g, 10 mmoles) with stirring for 0.5 hr. Solvent removal gave a residue
20 that was purified by flash chromatography on silica gel eluting with EtOH/H₂O/NH₄OH (9:1:1) to give pure 2-16.

¹H NMR (300 MHz, CD₃OD) δ 0.5 (3H, t), 0.92 (5H, m), 1.05-1.45 (6H, m), 1.70 (2H, bd), 1.91 (2H, t), 2.65 (2H, t), 2.98 (4H, m), 3.06 (2H, bd), 3.14 (2H, t), 3.42 (2H, m), 7.23 (1H, t), 7.63 (2H, d), 7.90 (s).
25



[N-2-(N'-BOC-4-Piperidinyl)ethyl]-N''-3-[methyl 2(S)-thien-2-ylsulfonylaminopropionate]-1,3-benzenedicarboxamide (2-18)

A solution of 2-2 (0.34 g, 0.71 mmoles) in CH₂Cl₂ (5 ml) at room temperature was treated with pyridine (2.12 mmoles) followed by 2-thiophenesulfonylchloride (Aldrich) (0.32 g, 2.12 mmoles). After stirring for 3 hours, the solvent was removed and the residue was taken up in CH₂Cl₂ washed with NaHCO₃, 10% KHSO₄, brine, dried (MgSO₄) and concentrated. The residue was purified by flash chromatography on silica gel eluting with 5% MeOH/CHCl₃ to provide pure 2-18, R_f 0.45 (silica, 10% MeOH/CHCl₃(NH₃)).

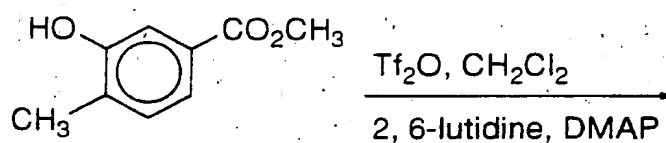
- 45 -

[N-2-(4-Piperidiny)ethyl]-N'-[3-2(S)-thien-2-yl-sulfonylamino-propionic acid]-1,3-benzenedicarboxamide (2-19).

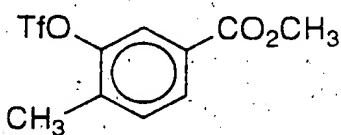
Treatment of 2-18 with LiOH·H₂O followed by deprotection with HCl gas in EtOAc as described for 3-4 gave 2-19 as a white solid. R_f 0.23 (silica, EtOH, NH₄OH/H₂O (10:1:1)).

¹H NMR (300 MHz, CD₃OD) δ 1.40 (2H, m), 1.66 (2H, m), 1.77 (1H, m), 2.04 (2H, bd), 3.00 (2H, t), 3.50 (2H, t), 3.65 (2H, m), 3.77 (2H, dd), 3.90 (2H, dd), 7.10 (1H, m), 7.59 (2H, m), 7.72 (1H, d), 7.98 (2H, m), 8.26 (1H, s).

Preparation of Dimethyl 4-methylbenzene-1,3-dicarboxylate (2-20)



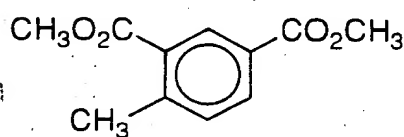
(2-20a)



(2-20b)

25

CO, Pd(OAc)₂,
dppp, CH₃OH,
DMSO, Et₃N



(2-20)

Methyl 4-methyl-3-trifluoromethanesulfonyloxybenzoate (2-20b)

A solution of methyl 4-methyl-3-hydroxybenzoate (2-20a) (20.0 g, 0.12 moles) [prepared from the corresponding carboxylic acid (Aldrich) by treatment with a methanolic solution of HCl gas] in CH₂Cl₂ (900 ml) was cooled to -40°C and treated successively with 2,6-lutidine (0.18 moles), DMAP (2.9 g, 0.024 moles) and trifluoromethylsulfonyl anhydride (0.18 moles). The cooling bath was then removed and the resulting mixture was stirred at ambient temperature for 2.0 hours. The solvent was then removed and the residue was purified by flask chromatography on silica eluting with hexane(8)/-EtOAc(2) to provide pure 2-20b, R_f 0.35.

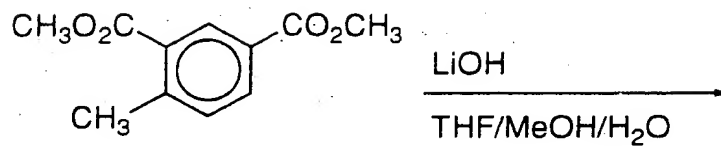
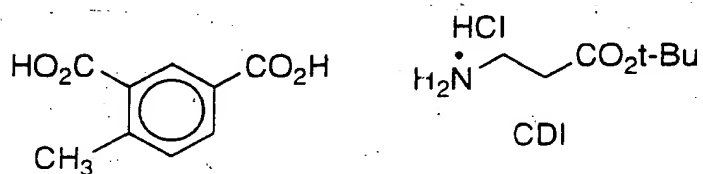
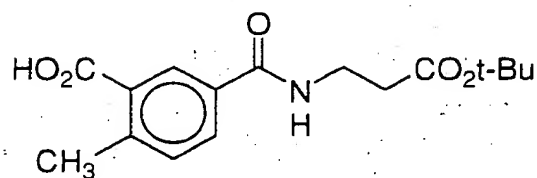
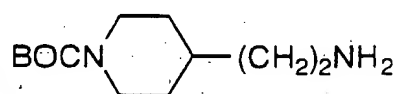
¹H NMR (300 MHz, CDCl₃) δ 2.18 (3H, s), 3.85 (3H, s), 7.30 (1H, d), 7.84 (1H, s), 7.90 (1H, d).

Dimethyl 4-methylbenzene-1,3-dicarboxylate (2-20)

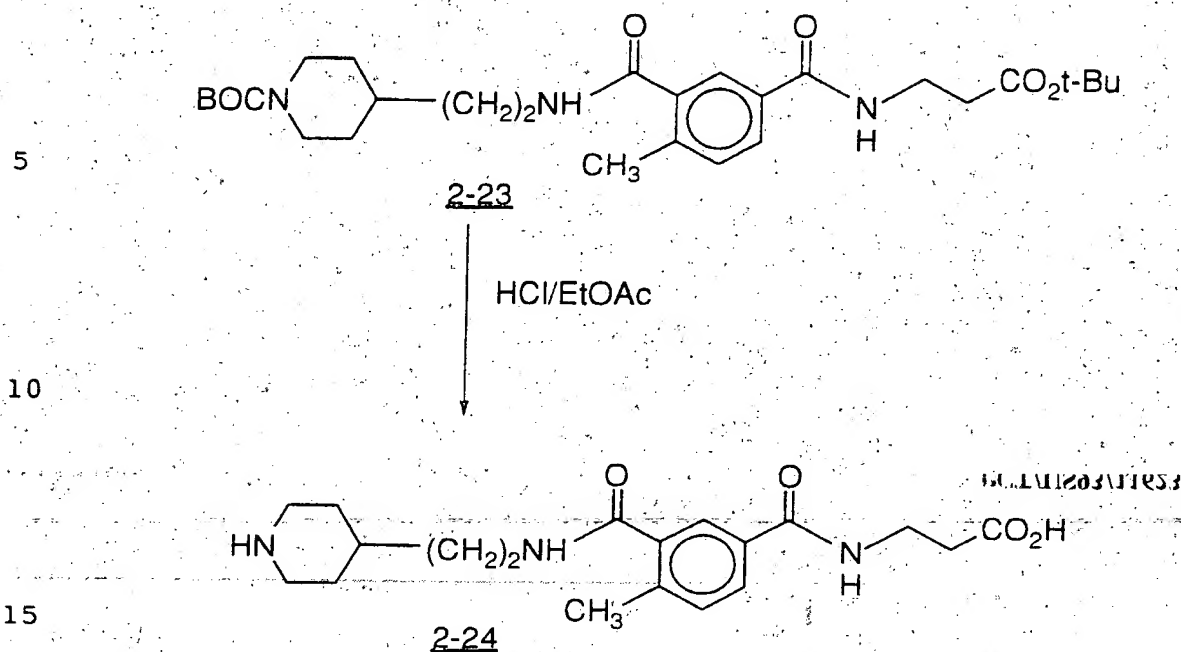
A solution of 2-20b (30.0 g, 0.121 moles) in methanol/300 ml was treated successively with DMSO (180 ml), triethylamine (0.278 moles), palladium acetate (0.807 g, 3.6 mmols) and dppp (1.48 g, 3.6 mmols) as the reaction turned to a clear dark brown solution. Carbon monoxide was then bubbled through the reaction mixture for 3 minutes and the resulting mixture was heated at reflux, while continuing to bubble CO. After refluxing for 4 hours the reaction mixture was concentrated and the resulting brown oil was purified by flask chromatography on silica gel eluting with hexane(90)/EtOAc(10) to provide pure 2-20.

¹H NMR (300 MHz, CDCl₃) δ 2.69 (3H, s), 3.95 (3H, s), 3.96 (3H, s), 7.37 (1H, d), 8.09 (1H, dd), 8.60 (1H, d).

- 47 -

2-202-212-22BOP/CH₃CN1-6

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4-Methyl-1,3-benzenedicarboxylic acid (2-21)

A solution of 2-20 (1.5 g, 7.2 mmol) in THF/MeOH/H₂O (1:1:1) (36 ml) at room temperature was treated with LiOH·H₂O (1.5 g, 36 mmol). After stirring for 3 hours, the solvent was removed and the residue acidified with 1N HCl. This was extracted with EtOAc, and the extract was dried (MgSO₄) and concentrated to give 2-21.
¹H NMR (300 MHz, CD₃OD) δ 2.65 (3H, s), 7.40 (1H, d), 8.03 (2H, d), 8.56 (1H, s).

4-Methyl-3-carboxy-N-2-(t-butyloxycarbonyl)ethyl-benzenecarboxamide (2-22)

2-21 (0.4 g, 2.22 mmol) in DMF (6 ml) was treated at room temperature with CDI (4.44 mmol). After stirring for 10 minutes, β-alanine t-butylester HCl (Bachem) (0.20 g, 1.11 mmol) was added and the reaction mixture was stirred for 18 hours. The solvent was removed and the residue acidified to pH 2-3 with 10% KHSO₄ solution extracted with EtOAc and this was dried (MgSO₄) and

- 49 -

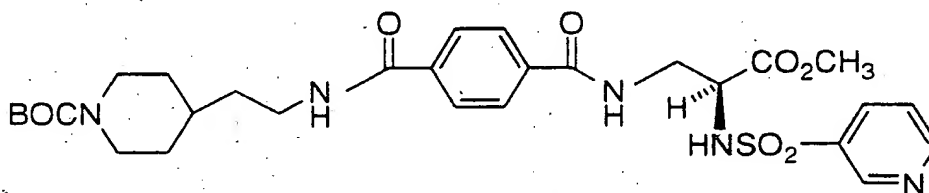
concentrated. The residue was purified by flash chromatography on silica gel eluting with CH₂Cl₂/MeOH/HOAc (9/0.25/0.25).

4-Methyl-3-{N-[2-(N'-Boc-4-piperidinyl)ethyl]-N''-2-(t-butyloxy-carbonyl)ethyl}-1,3-benzenedicarboxamide (2-23)

A solution of 2-22 (0.33 g, 1.07 mmoles) in CH₃CN (5 ml) was treated with 1-6 (0.38 g, 1.6 mmoles) at room temperature to give a clear solution. This was treated with NMM (2.7 mmoles) followed by BOP (1.6 mmoles) and the reaction mixture was stirred for 18 hours. This was then diluted with EtOAc, washed with H₂O, 10% KHSO₄, saturated NaHCO₃, brine, dried (MgSO₄) and concentrated. The residue was purified by flash chromatography on silica gel eluting with 60% EtOAc/hexanes to give pure 2-23. R_f 0.26 (silica, 60% EtOAc/hexanes).

4-Methyl-[2-(4-piperidinyl)ethyl]-N'-2-(carboxyethyl)-1,3-benzenedicarboxamide (2-24)

A solution of 2-23 (0.23 mmoles) in EtOAc (5 ml) was treated with HCl gas as described for 3-4 to give 2-24 as a white solid. ¹H NMR (300 MHz, D₂O) δ 1.12 (2H, t), 1.33 (2H, m), 1.52 (2H, m), 1.60 (1H, m), 1.90 (2H, bd), 2.26 (3H, s), 2.58 (2H, t), 2.88 (2H, bt), 3.32 (4H, m), 3.52 (2H, t), 7.29 (1H, d), 7.52 (1H, s), 7.59 (1H, dd).



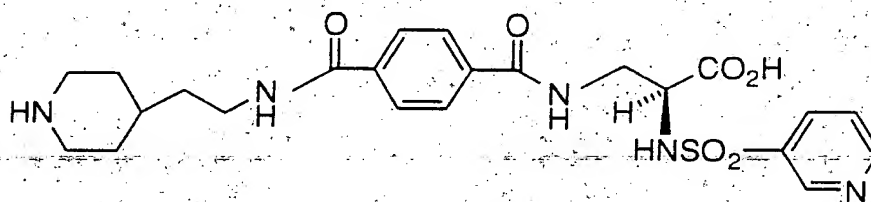
2-25

{N-2-(N'-Boc-4-piperidinylethyl)-N''-3-[methyl 2(S)-(3-pyridyl-sulfonylamino)propionate]}-1,4-benzene dicarboxamide (2-25)

- 50 -

Compound 2-25 was prepared using the same procedure as for 2-2, utilizing 1-6, terephthalic acid and 9-13. R_f 0.26 (60% Acetone/Hexane).

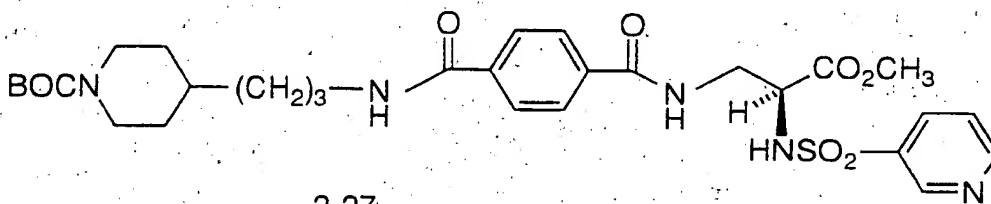
¹H NMR (300 MHz, CDCl₃) δ 9.1 (s, 1H), 8.8 (d, J = 3 Hz, 1H), 8.2 (m, 1H), 7.9 (m, 1H), 7.7 (s, 4H), 7.5 (m, 1H), 7.4 (m, 1H), 4.4 (m, 1H), 4.1 (bd, 2H), 3.9 (s, 2H), 3.7 (s, 3H), 3.6 (m, 2H), 2.8 (m, 2H), 1.9 - 1.6 (m, 5H), 1.6 (s, 9H), 1.2 (m, 2H).

2-26

{N-2-(4-Piperidylethyl)-N'-3-[2(S)-(3-pyridylsulfonylamino)-propanoic acid]-1,4-benzenedicarboxamide (2-26)}

Compound 2-25 was treated with 6N HCl at room temperature for 16 hours, then concentrated to yield 2-26 as a white solid. R_f 0.27 (9:1:1 EtOH/H₂O/NH₄OH).

¹H NMR (300 MHz, D₂O) δ 9.1 (s, 1H), 8.7 (m, 2H), 7.9 (dd, J = 6, 8 Hz, 1H), 7.8 (d, J = 8.5, 2H), 7.7 (d, J = 8.5, 2H), 4.5 (dd, J = 4, 9 Hz, 1H), 3.8 (dd, J = 4, 14 Hz, 1H), 3.5 (dd, J = 9, 14 Hz, 1H), 3.4 (m, 4H), 3.0 (m, 2H), 1.95 (bd, 2H), 1.8-1.6 (m, 3H), 1.4 (m, 2H).

2-27

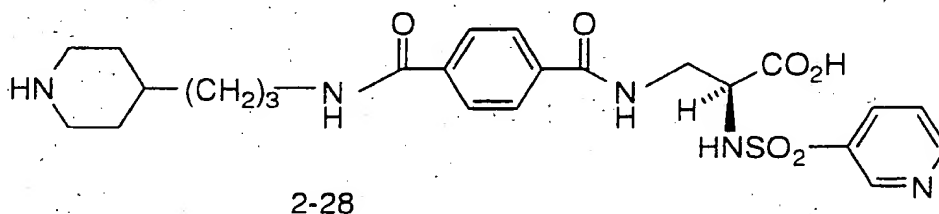
{N-3-(N'-BOC-4-piperidylpropyl)-N''-3-[methyl 2(S)-(3-pyridylsulfonylamino)propionate]}-1,4-benzene dicarboxamide (2-27)

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Compound 2-27 was prepared using the same procedure as for 2-25, utilizing 9-13, terephthalic acid and 3-(4-N-BOC-piperidiny) propylamine (Compound 10-1, page 50, line 2, and page 51, lines 53-54, of European Publication 540,334).

R_f 0.26 (60% Acetone/Hexanes)

¹H NMR (300 MHz, CDCl₃) δ 9.0 (s, 1H), 8.7 d, (1H), 8.1 (m, 1H), 7.6 (s, 4H), 7.4 (dd, 1H), 7.0 (bt, 1H), 4.3 (m, 1H), 4.0 (bd, 2H), 3.8 (s, 3H), 3.4 (m, 2H), 2.6 (bt, 2H), 1.6 (bd, 4H), 1.4 (s, 9H), 1.3-1.2 (m, 3H), 1.1 (m, 2H).

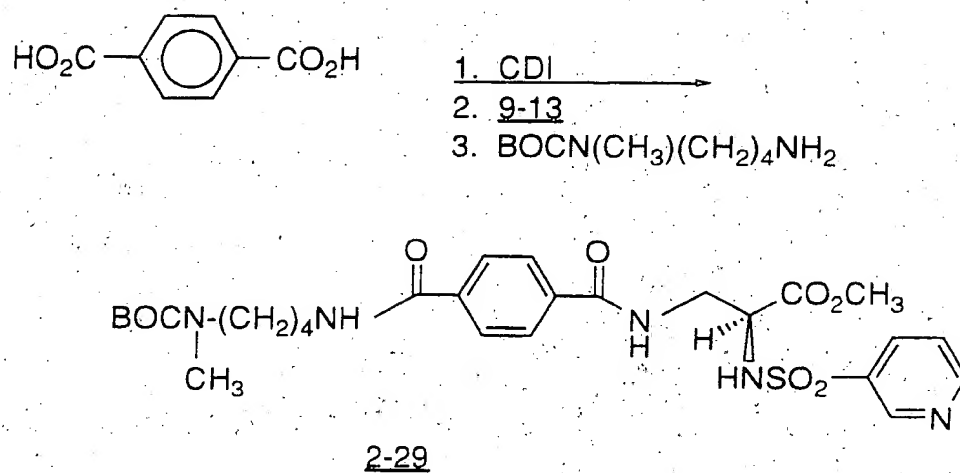


{N-3-(4-Piperidiny)propyl)-N'-3-[2(S)-3-pyridylsulfonylamino-propanoic acid]-1.4-benzendicarboxamide (2-28)

Compound 2-28 was prepared using the same procedure as described for 2-26. R_f 0.27 (9:1:1 EtOH/H₂O/NH₄OH).

¹H NMR (300 MHz, D₂O) δ 9.2 (s, 1H), 8.7 (m, 2H), 7.9 (m, 1H), 7.7 (d, J = 8.5 Hz, 1H), 7.65 (d, J = 8.5 Hz, 1H), 4.45 (dd, J = 4, 9 Hz, 1H), 3.8 (dd, J = 4, 14 Hz, 1H), 3.5 (dd, J = 9, 14 Hz, 1H), 3.4 (m, 4H), 3.0 (m, 2H), 1.9 (bd, 2H), 1.6 (m, 3H), 1.4 (m, 4H).

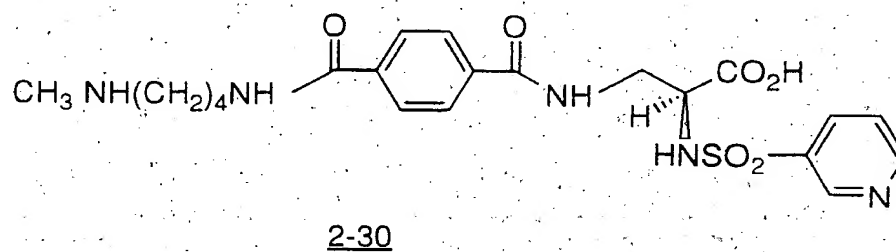
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4-[4-(N-Boc-N-Methylamino)butylaminocarbonyl]benzoyl-2(S)-3-pyridylsulfonylamino-β-alanine methyl ester (2-29)

Treatment of 1,4-benzene dicarboxylic acid (Aldrich) with CDI, 9-13 and 4-(N-t-butyloxycarbonyl methyl amino)butylamine (Syn. Comm., 1992, 22, 2357) as described for 1-2 gave 2-29.

¹H NMR (300 MHz, CDCl₃) δ 9.0 (s, 1H), 8.71 (d, 1H), 8.11 (m, 1H), 7.8-7.6 (m, 4H), 7.58 (m, 1H), 7.35 (dd, 1H), 4.3 (t, 1H), 3.8 (m, 2H), 3.6 (s, 3H), 3.45 (m, 2H), 3.25 (bs, 2H), 2.8 (s, 3H), 1.6 (bs, 4H), 1.45 (s, 9H).



4-[(4-(N-Methylaminobutyl)aminocarbonyl]benzoyl-2(S)-3-pyridylsulfonylamino-β-alanine (2-30)

Treatment of 2-29 with 6N HCl, followed by concentration and column chromatography (SiO₂, 9:1:1 EtOH/H₂O/NH₄OH) gave 2-30 as a white solid.

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^1H NMR (300 MHz, D_2O) δ 8.7 (s, 1H), 8.15 (d, 1H), 8.0 (d, 1H), 7.75 (d, 2H), 7.6 (d, 2H), 7.2 (m, 1H), 3.7 (dd, 1H), 3.6 (dd, 1H), 3.4 (m, 2H), 3.2 (dd, 1H), 2.5 (m, 2H), 2.25 (s, 3H), 1.7-1.4 (m, 4H).

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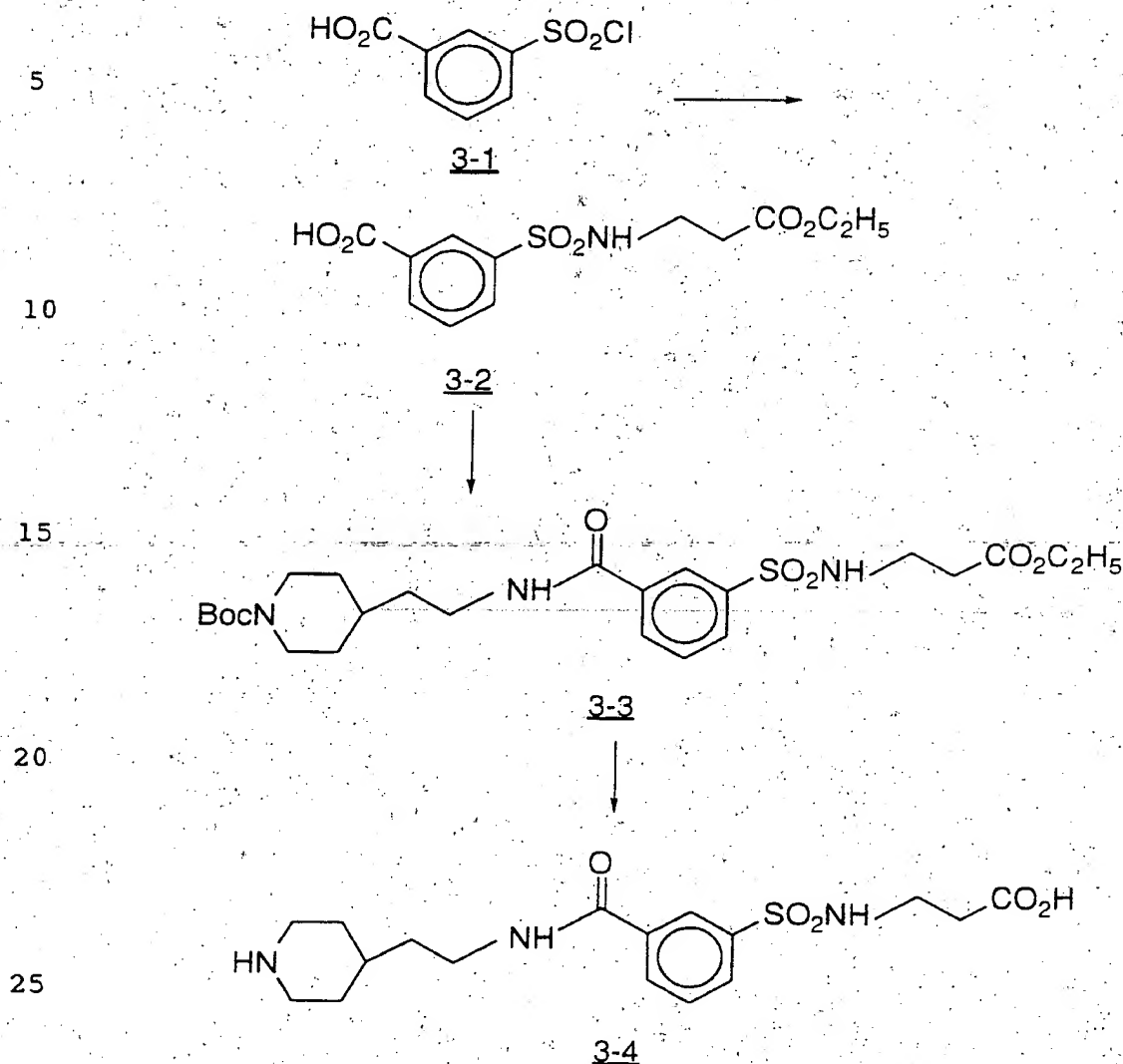
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SCHEME 3



3-[(2-Carboethoxyethyl)aminosulfonyl]benzoic acid (3-2)

30 To a solution of 3-chlorosulfonylbenzoic acid (3-1) (Maybridge Chemicals) (1.10g, 5 mmoles) and β -alanine ethyl ester (0.85g, 5.5 mmoles) in CHCl_3 (20 ml) at room temperature was added triethylamine (1.52g, 15 mmoles). After stirring for 3 hrs the solvent was removed, the residue was taken up in EtOAc, washed with H_2O , 10% KHSO_4 solution, H_2O , brine and dried (Na_2SO_4) Solvent

- 55 -

removal gave a residue that was purified by flash chromatography on silica gel eluting with $\text{CHCl}_3(97)/\text{MeOH}(3)$ to give pure 3-2.

^1H NMR (300 MHz, CDCl_3) δ 1.24 (3H, t), 2.55 (2H, t), 3.23 (2H, q), 4.25 (2H, q), 6.66 (1H, t), 7.65 (1H, t), 8.12 (1H, d), 8.30 (1H, d), 8.60 (1H, s).

3-[(2-Carboethoxyethyl)aminosulfonyl]-N-[N'-2-(Boc-4-piperidinyl-ethyl)]benzamide (3-3)

To a solution of 3-2 (0.3g, 1 mmole) and 1-6 (0.228g, 1 mmole) in acetonitrile (15 ml) was added BOP (0.53g, 1.2 mmole) and triethylamine (0.36g, 3.6 mmole) at room temperature. After stirring for 48 hours the solvent was removed and the residue was taken up in EtOAc and this was washed with H_2O , 10% KHSO_4 solution, H_2O , saturated NaHCO_3 solution, brine and dried (Na_2SO_4). Solvent removal provided a residue that was triturated with Et_2O to give 3-3 as a viscous, yellow residue.

^1H NMR (300 MHz, CDCl_3) δ 1.0-1.22 (2H, m), 1.22 (3H, t), 1.45 (9H, bs), 1.45-1.80 (5H, m), 2.52 (2H, t), 2.65 (2H, bt), 3.22 (2H, m), 3.49 (2H, m), 3.95-4.20 (4H, m), 5.69 (1H, bt), 6.80 (1H, bt), 7.60 (1H, t), 7.98 (1H, d), 8.06 (1H, d), 8.23 (1H, s).

3-[(2-Carboxyethyl)aminosulfonyl]-N-[2-(4-piperidinyl-ethyl)]benzamide (3-4)

3-3 (0.44g, 0.86 mmole) was dissolved in 15 ml of $\text{THF}(1)/\text{MeOH}(1)/\text{H}_2\text{O}(1)$, treated with $\text{LiOH}\cdot\text{H}_2\text{O}$ (3.0 mmole), and this was stirred at room temperature for 16 hrs. The solvent was then removed and the residue was taken up in 100 ml/ H_2O and this acidified to pH 2-3 with 10% KHSO_4 soln. This solution was extracted with EtOAc and the combined extracts were washed with brine and dried (Na_2SO_4). Solvent removal gave a residue that was purified by flash chromatography on silica gel eluting with $\text{CHCl}_3(95)/\text{MeOH}(5)$ to give the desired acid as an oil.

^1H NMR (300 MHz, CDCl_3) δ 1.0-1.21 (2H, m), 1.46 (9H, bs), 1.46-1.78 (5H, m), 2.53 (2H, t), 2.68 (2H, bt), 3.20 (2H, m), 3.50 (2H, bq),

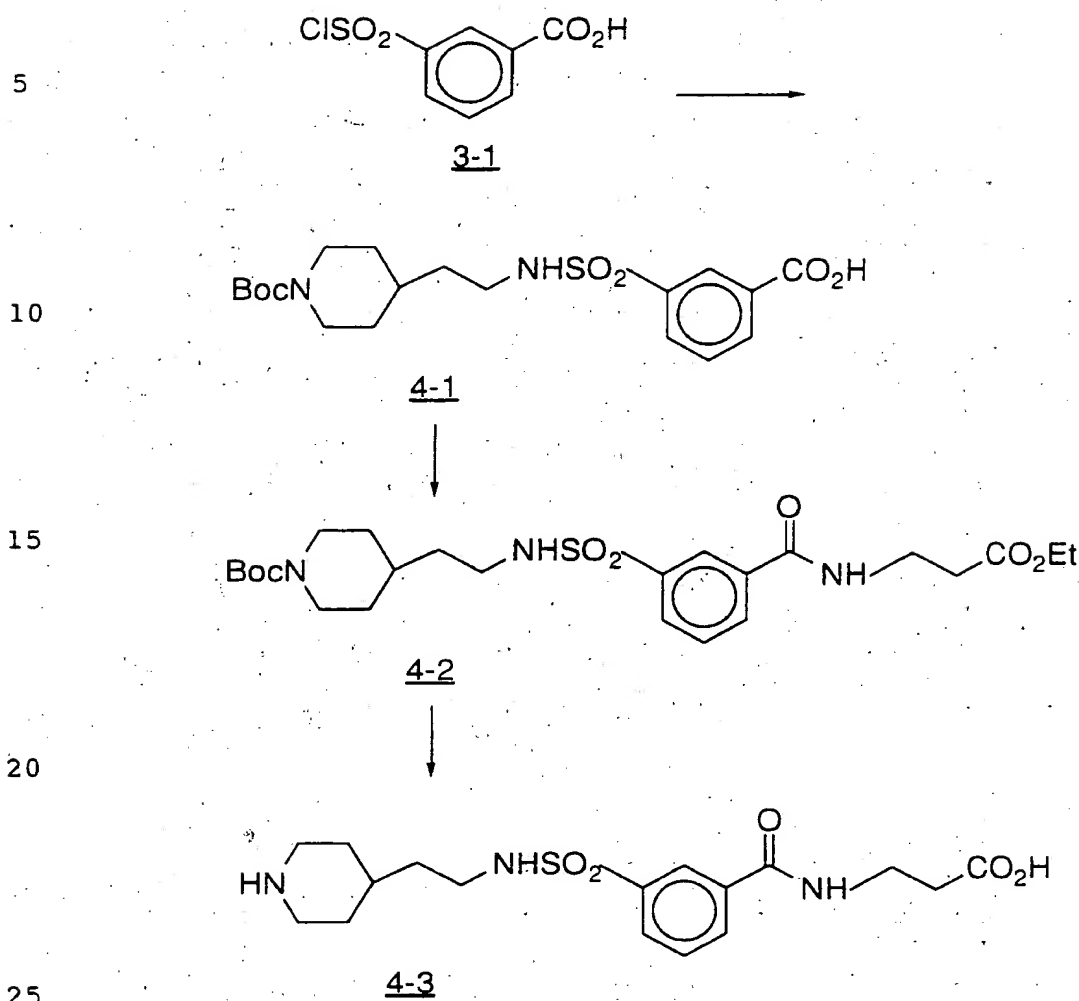
- 56 -

4.05 (2H, bd), 6.08 (1H, b), 6.89 (1H, bt), 7.60 (1H, t), 8.01 (1H, d),
8.05 (1H, d), 8.27 (1H, s).

This acid was dissolved in EtOAc (30ml), cooled to -25°C and treated by bubbling gaseous HCl through the solution for 20 minutes. The reaction mixture was then stoppered and stirred at 0°C for 1.0 hr. The solvent was removed and the resulting solid was triturated with EtOAc (30 ml) to give crude 3-4 as a white solid. This was purified by flash chromatography on silica gel eluting with H₂O(1)/NH₄OH(1) to give pure 3-4.

¹H NMR (300 MHz, CD₃OD) δ 1.30-1.53 (2H, m), 1.53-1.82 (3H, m), 2.0 (2H, bd), 2.30 (2H, t), 2.95 (2H, dt), 3.10 (2H, t), 3.35 (2H, bd), 3.48 (2H, t), 7.68 (1H, t), 8.01 (1H, d), 8.05 (1H, d), 8.30 (1H, s).

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SCHEME 43-[2-(N-Boc-Piperidin-4-yl)ethylaminosulfonyl]benzoic acid (4-1)

30 A solution of 2-(N-Boc-4-piperidinyl)ethyl-amine (1-6) (0.45g, 2.0 mmoles) in CHCl_3 (20 ml) was treated with added triethylamine (0.405g, 4.0 mmoles) followed by 3-chlorosulfonylbenzoyl chloride (3-1) (0.44g, 2.0 mmoles) and the resulting solution was stirred at room temperature for 16 hours. The solvent was then removed and the residue was taken up in EtOAc and washed with H_2O , 10% KHSO_4 solution, brine and dried (Na_2SO_4). Solvent removal

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provided a residue that was purified by flash chromatography on silica gel eluting with $\text{CHCl}_3(95)/\text{MeOH}(5)$ to give pure 4-1.

^1H NMR (300 MHz, CDCl_3) δ 0.98-1.2 (2H, m), 1.46 (9H, bs), 1.3-1.7 (5H, bd), 2.64 (2H, dt), 3.04 (2H, m), 4.05 (2H, bd), 5.04 (1H, bs), 7.65 (1H, t), 8.12 (1H, d), 8.31 (1H, d), 8.6 (1H, s).

3-[2-(N-Boc-4-Piperidinyl)ethylaminosulfonyl]-N'-[(2-carboethoxy)-ethyl]benzamide (4-2)

A solution of 4-1 (0.7g, 1.7 mmol), β -alanine ethyl ester hydrochloride (0.26g, 1.7 mmol), BOP (0.90g, 2.04 mmol) in CH_3CN (15 ml) was treated with 0.62g (6.12 mmol) triethylamine and the resulting solution was stirred at room temperature for 16 hours. The solvent was removed and the residue was dissolved in EtOAc. This was washed with H_2O , 10% KHSO_4 solution, H_2O , saturated NaHCO_3 solution, brine and dried (Na_2SO_4). Solvent removal provided a residue that was purified by flash chromatography on silica gel eluting with CHCl_3 (96)/ MeOH (4) to give pure 4-2.

^1H NMR (300 MHz, CDCl_3) δ 0.91-1.12 (2H, m), 1.27 (3H, t), 1.27-1.62 (5H, m), 1.45 (9H, bs), 2.49-2.72 (4H, m), 2.9-3.05 (2H, m), 3.72 (2H, q), 4.02 (2H, bd), 4.15 (2H, q), 5.35 (1H, bs), 7.122 (1H, bt), 7.59 (1H, t), 7.99 (2H, d), 8.3 (1H, s).

3-[2-(4-Piperidinyl)ethylaminosulfonyl]-N-[(2-carboxyethyl)]benzamide (4-3)

4-2 (0.17g, 4.05 mmol) was dissolved in 15 ml of $\text{THF}(1)/\text{MeOH}(1)/\text{H}_2\text{O}(1)$, treated with $\text{LiOH}\cdot\text{H}_2\text{O}$ (12 mmol), and this was stirred for 16 hours. The solvent was then removed and the residue was diluted with H_2O (100 ml) and extracted with Et_2O . The aqueous phase was adjusted to pH 2-3 with 10% KHSO_4 and extracted with EtOAc. The organic phase was washed with brine, dried (Na_2SO_4) and the solvent removed to give the desired acid. R_f 0.15 (silica gel, $\text{CHCl}_3(95)/\text{MeOH}$ (5)).

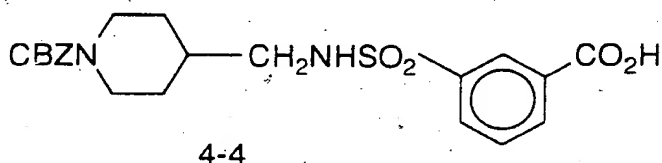
^1H NMR (300 MHz, CDCl_3) δ 0.87-1.1 (2H, m), 1.22-1.55 (5H, m), 1.44 (9H, bs), 2.55 (2H, bt), 2.75 (2H, m), 2.98 (2H, m), 3.72 (2H, m),

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4.00 (2H, bd), 5.42 (1H, bs), 7.62 (1H, t), 7.65 (1H, bs), 8.00 (1H, d), 8.17 (1H, d), 8.34 (1H, s).

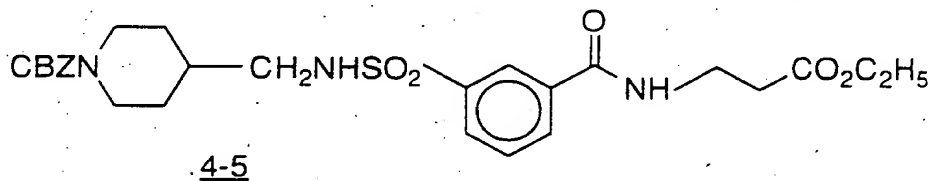
This acid (0.48g, 1.0 mmole) was dissolved in EtOAc and treated with HCl gas as described for 3-4. Trituration of crude product with EtOAc gave pure 4-3, R_f 0.35 (silica gel/EtOH(9)/H₂O(1)).

¹H NMR (300 MHz, CD₃OD) δ 1.20-1.39 (2H,m), 1.45 (2H,q), 1.72 (1H,m), 1.88 (2H,bd), 2.65 (2H,t), 2.74-3.03 (4H,m), 3.35 (2H,bd), 3.64 (2H,q), 7.68 (1H,t), 8.02 (2H,m), 8.28 (1H,s), 8.80 (1H,bt)



3-[N-CBZ-4-Piperidinyl)methylaminosulfonyl]benzoic acid (4-4)

4-4 was prepared as described for 4-1 wherein (N-CBZ-piperidin-4-yl)methylamine 8-3 was employed. 4-1 had ¹H NMR (300 MHz, CD₃OD) δ 0.95-1.13 (2H, m), 1.52-1.75 (3H, m), 2.72 (2H, d), 2.60-2.90 (2H, m), 4.10 (2H, d), 5.09 (2H, s), 7.2-7.4 (5H, m), 7.66 (1H, t) 8.02 (1H, d), 8.22 (1H, d), 8.44 (1H, d)



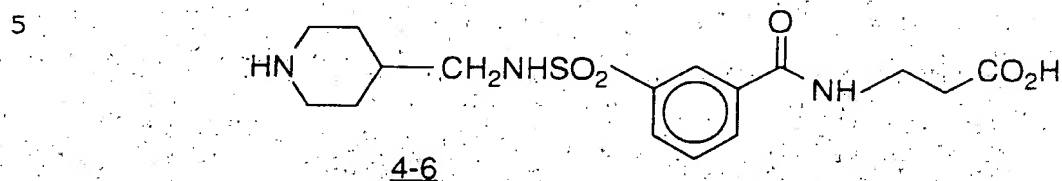
3-[(N-CBZ-4-Piperidinyl)methylaminosulfonyl]-N'-[(2-carboethoxy)ethyl]benzamide (4-5)

4-5 was prepared as described for 4-2.

¹H NMR (300 MHz, CDCl₃) δ 0.96-1.16 (2H, m), 1.26 (2H, t), 1.52-1.73 (3H, bd), 2.65 (2H, t), 2.60-2.70 (2H, m), 2.72 (2H, t), 3.72 (2H,

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q), 4.13 (4H, bq), 5.09 (2H, s), 5.30 (1H, bt), 7.17 (1H, bt), 7.25-7.45 (5H, m), 7.59 (1H, t), 7.97 (2H, d), 8.28 (1H, s)



10 3-[(4-Piperidinyl)methylaminosulfonyl]-N-[(2-carboxyethyl)]benzamide
(4-6).

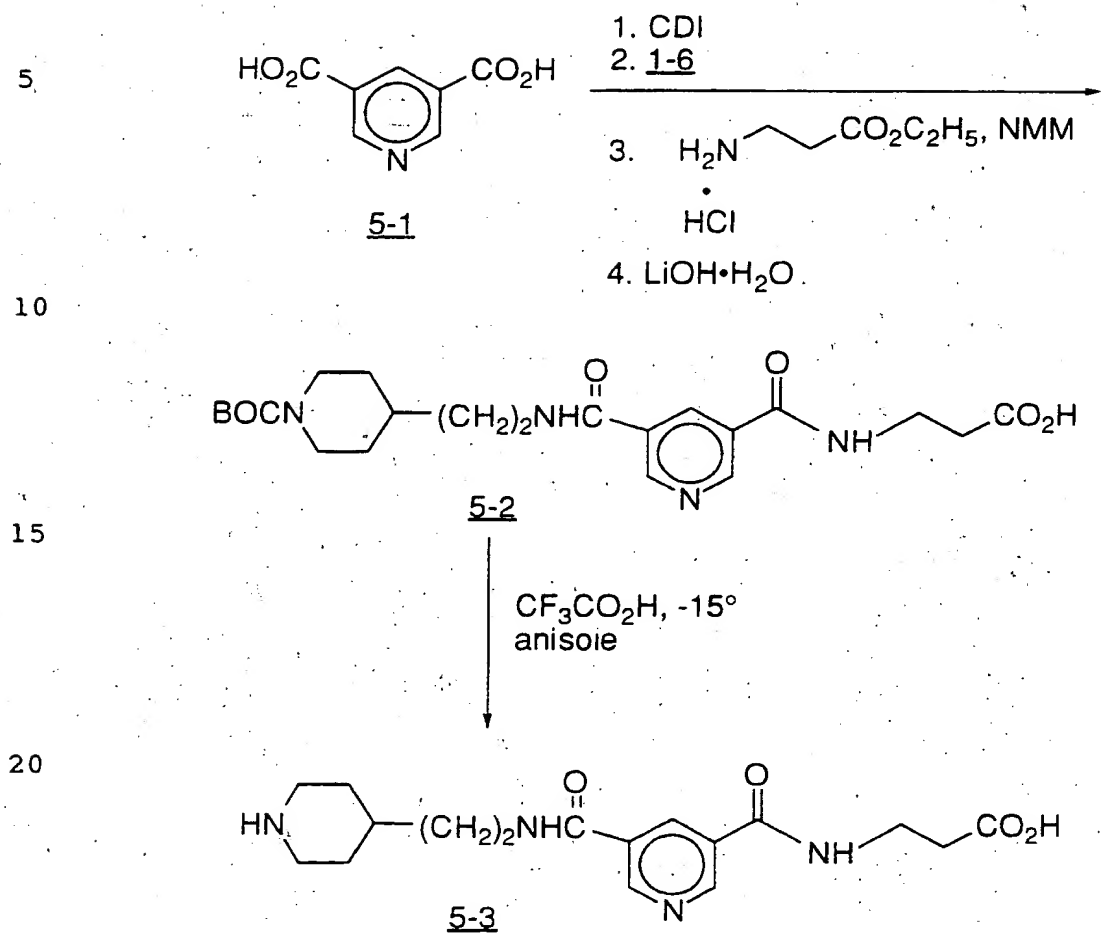
15 4-6 was prepared from 4-5 as described for 4-3.
¹H NMR (300 MHz, CD₃OD) δ 1.25-1.50 (2H, m), 1.74 (1H, m), 1.88
(2H, bd), 2.49 (2H, t), 2.80-2.96 (4H, m), 3.34 (2H, bd), 3.63 (2H, t),
7.65 (1H, t), 7.98 (1H, d), 8.04 (1H, d), 8.27 (1H, s).

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SCHEME 5

N-[(2-(N-Boc-4-Piperidiny)ethyl)-N'-[(2-carboxyethyl)-3,5-pyridine-dicarboxamide (5-2)]

A solution of 3,5-pyridinedicarboxylic acid (Aldrich) (5-1) (0.74g, 4.4 mmoles) in DMF (40 ml) at room temperature was treated with carbonyldiimidazole (CDI) (1.4g, 8.8 mmoles) and after 1 hr, 1-6 (4.4 mmoles) was added. Then, β-alanine ethyl ester hydrochloride (0.67g, 4.4 mmoles) was added followed by N-methylmorpholine (NMM) (13.2 mmoles) and the resulting solution was stirred at room temperature for 16 hrs. The reaction was diluted with EtOAc and washed with H₂O, 10% KHSO₄ solution, brine and dried (Na₂SO₄).

Solvent removal provided the desired dicarboxamide as an oil, which was submitted without further purification to the next reaction.

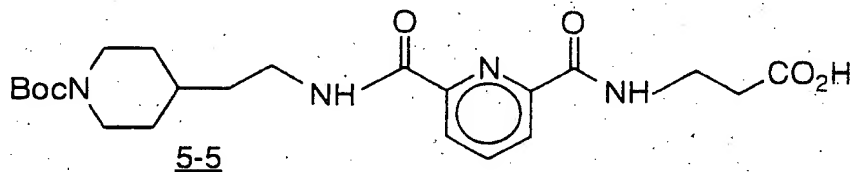
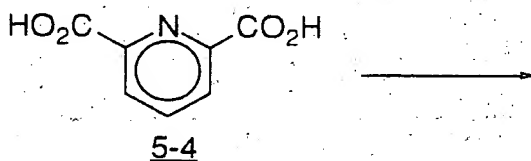
This oil was dissolved in THF(1)/MeOH(1)/H₂O(1) (15 ml) and LiOH (21 mmoles) was added. After stirring at room temperature for 1 hr the reaction mixt was diluted with EtOAc/H₂O. The aqueous phase was separated and adjusted to pH 5 with 10% KHSO₄ soln and extracted with EtOAc. The organic phase was washed with H₂O, brine and dried (Na₂SO₄). Solvent removal gave the desired acid (5-2) as a white solid.

¹H NMR (300 MHz, CD₃OD) δ 8.99 (s, 2H); 8.52 (s, 1H), 4.95 (d, 2H), 3.58 (t, 2H), 3.40 (m, 2H), 2.75-2.60 (m, 2H), 2.58 (t, 2H), 1.7 (d, 2H), 1.5 (m, 3H), 1.37 (s, 9H), 1.05 (m, 2H).

N-[2-Piperidin-4-yl)ethyl]-N'-[(2-carboxy)ethyl]-3,5-pyridinedi-carboxamide (5-3)

5-2 (0.30g, 0.67 mmols) was dissolved in CH₂Cl₂ and treated at -15° with anisole (1.5 mmols) and trifluoroacetic acid (3 ml). After stirring for 0.5 hour, the solvent was removed and the residue was purified by flash chromatography on silica gel eluting with MeOH(10)/NH₄OH(1)/H₂O(1) to provide 5-3.

¹H NMR (330 MHz, D₂O) δ 9.02 (m, 2H), 8.48 (s, 1H), 3.63 (t, 2H), 3.51 (t, 2H), 3.45 (d, 2H), 3.01 (dt, 2H), 2.5 (t, 2H), 2.03 (d, 2H), 1.75 (m, 1H), 1.68 (q, 2H), 1.45 (m, 2H).

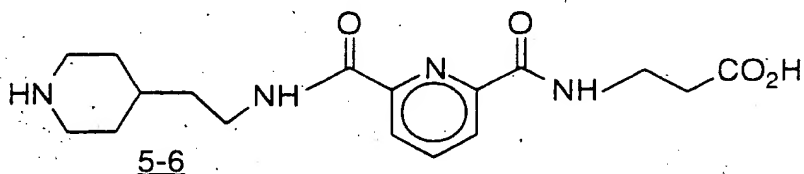


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N-[2-(N'-Boc-4-Piperidiny)ethyl]-N'-[(2-carboxy)ethyl]-2,6-pyridine-dicarboxamide (5-5)

5-5 was prepared from 2,6-pyridinedicarboxylic acid (Aldrich) as described for 5-2. 5-5 had ^1H NMR (300 MHz, CDCl_3) δ 8.54 (t, 1H), 8.40 (d, 2H), 8.05 (t, 1H), 7.75 (m, 1H), 4.2 (m, 2H), 3.8 (m, 2H), 3.6 (m, 2H), 2.7 (m, 4H), 1.8-1.6 (m, 5H), 1.48 (s, 9H), 1.3 (m, 2H).

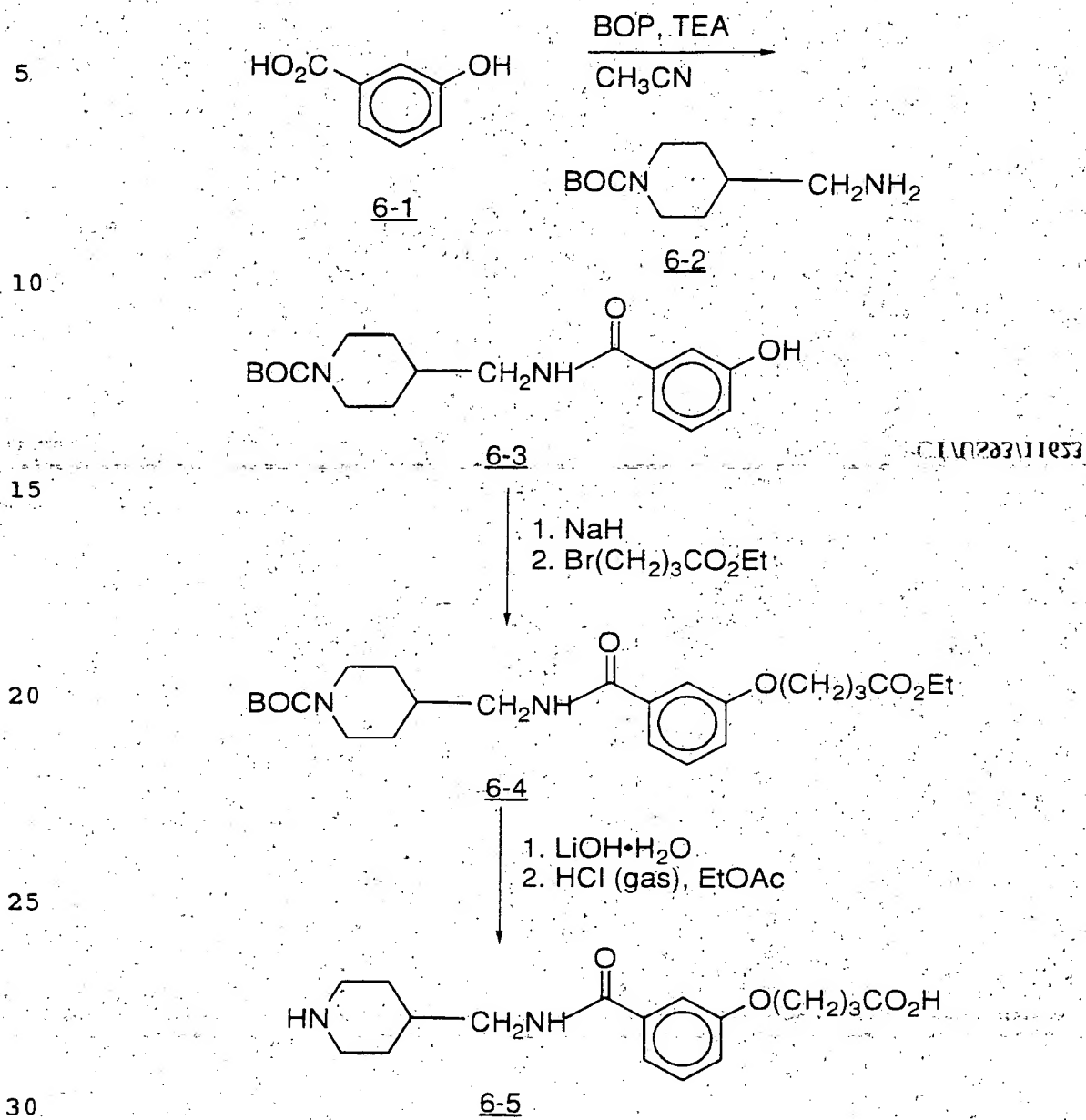
5-5 \longrightarrow



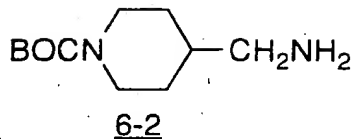
N-[2-(4-Piperidiny)ethyl]-N'-[(2-carboxy)ethyl]-2,6-pyridinedicarboxamide (5-6)

5-6 was prepared as described for 5-3. ^1H NMR (300 MHz, CD_3OD + DTFA) δ 8.06 (d, 2H), 7.94 (t, 1H), 3.50 (t, 2H), 3.33 (t, 2H), 3.18 (m, 2H), 2.78 (m, 2H), 2.48 (t, 2H), 1.88 (d, 2H), 1.5 (m, 3H), 1.22 (m, 2H).

SCHEME 6



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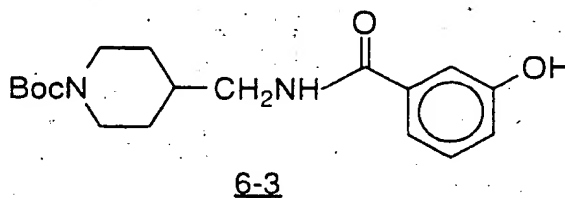


5

4-(N-t-Butyloxycarbonylpiperidinyl)methylamine (6-2)

A solution of 4-(piperidinyl)methylamine (Aldrich) (2-1) (22.8 g, 0.2 mmoles) in toluene (250 ml) was treated with benzaldehyde (21.2 g, 0.2 mmoles) at room temperature and the resulting mixture was heated at reflux for 3 hours with the aid of a Dean-Stark trap for water removal. The cooled reaction mixture containing the desired Schiff's base was treated portionwise with di-t-butyl dicarbonate (47.96 g, 0.22 moles) and the resulting solution was stirred at room temperature for 16 hours. The solvent was then removed and the residue was cooled to 0-5°C and treated with 1N KHSO₄ (220 ml) with stirring for 3 hours. The resulting reaction mixture was extracted with ether (3 x 200 ml) and then made basic with 1N KOH solution and extracted with CHCl₃ (4 x 75 ml). The combined organic extract was washed with brine, dried (Na₂SO₄) filtered through celite, and the solvent removed to provide pure 6-2 as a clear oil. ¹H NMR (300 MHz, CDCl₃) δ 1.13 (2H, m), 1.45 (9H, s), 1.60 (1H, m), 1.74 (2H, d), 2.68 (4H, m), 4.15 (2H, bd).

25



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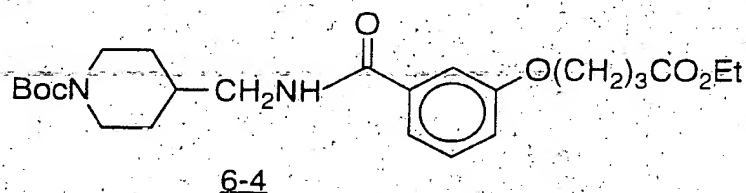
3-Hydroxy-N-[N'-Boc-4-(piperidinylmethyl)]carboxamide (6-3)

A suspension of 3-hydroxybenzoic acid (1.0 g, 7.24 mmoles) in CH₃CN (15 ml) at room temperature was treated with 6-2 (7.24 mmoles) and BOP (4.8 g, 10.8 mmoles) to give a homogenous

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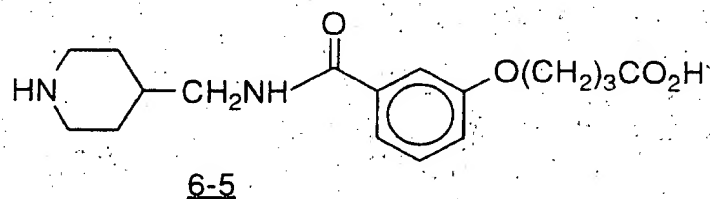
reaction mixture. TEA (21.7 mmoles) was added and this was stirred for 16 hours. The solvent was removed and the residue was taken up in EtOAc and washed with 10% KHSO₄ solution, brine and dried (MgSO₄). Solvent removal gave a residue that was purified by flash chromatography on silica gel eluting with 5% MeOH/CHCl₃ to give pure 6-3. R_f 0.8 (silica, 10% MeOH/CHCl₃ (NH₃)).

¹H NMR (300 MHz, CDCl₃) δ 1.14 (2H, m), 1.45 (9H, s), 1.70 (3H, m), 2.63 (2H, s), 3.31 (2H, b), 4.08 (2H, b), 6.58 (1H, t), 7.00 (1H, m), 7.22 (2H, m), 7.40 (1H, m).



3-(3-Carboethoxypropyloxy)-N-[N'-Boc-4(piperidinylmethyl)]-benzamide (6-4)

A solution of 6-3 (1.0 g, 2.99 mmoles) in DMF (15 ml) was treated with NaH (0.12 g, 2.99 moles) and, after 10 minutes stirring, the clear brown solution was treated with ethyl 4-bromobutyrate (3.3 mmoles). After 2 hours stirring at room temperature the solvent was removed and the residue was taken up in EtOAc, washed with H₂O, 10% KHSO₄ solution and brine. This was dried (MgSO₄), the solvent removed and the resulting residue purified by flash chromatography on silica gel eluting with 2% MeOH/CHCl₃ to give pure 6-4. R_f 0.6 (silica, 5% MeOH/CHCl₃).



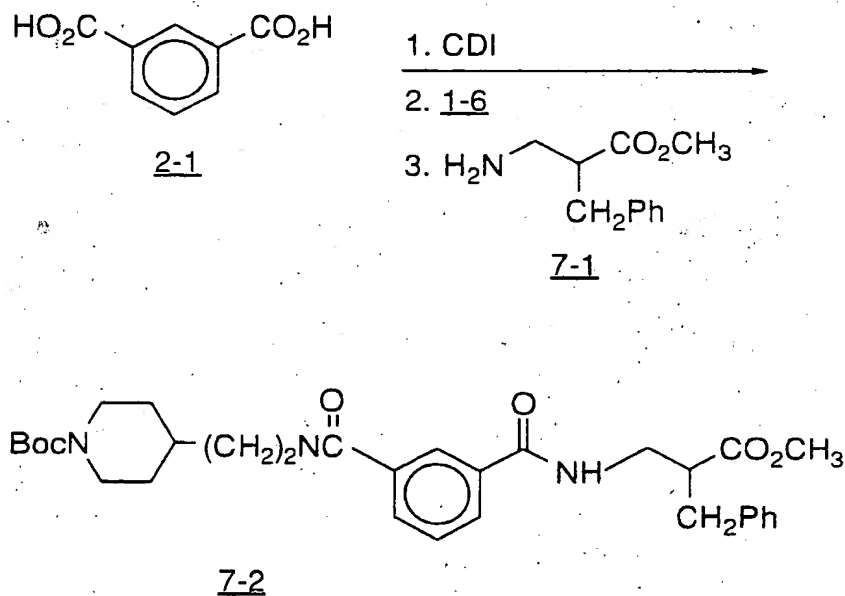
- 67 -

3-(3-Carboxypropyloxy)-N-(4-piperidinylmethyl)carboxamide (6-5)

A solution of 6-4 (0.49 g, 1.09 mmoles) in 15 ml of THF/MeOH/H₂O (1:1:1) was treated with LiOH·H₂O (0.23 g, 5.45 mmoles) as described for 1-3 to give the desired acid. R_f 0.7 (silica, 97:3:1 CHCl₃/MeOH/HOAc).

This acid was treated with HCl gas in EtOAc as described for 3-4 to give pure 6-5, R_f 0.34, silica (CHCl₃, CH₃OH, HOAc, 97/3/1).

¹H NMR (300 MHz, CD₃OD) δ 1.50 (2H, m), 1.99 (2H, bd), 2.08 (2H, m), 2.50 (2H, t), 2.98 (2H, bt), 3.31 (2H, m), 3.41 (2H, bd), 4.06 (2H, t), 7.10 (1H, m), 7.58 (3H, m).

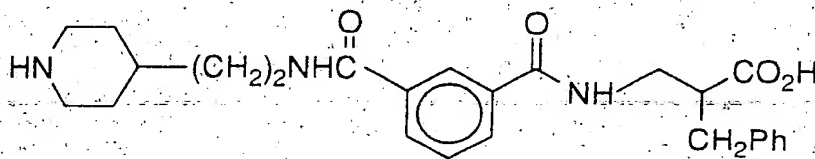
SCHEME 7

N-[2-(N'-Boc-4-piperidylethyl)]-N''-3-[methyl 2-benzyl-propionate]-1,3-benzenedicarboxamide (7-2)

- 68 -

Treatment of 2-1 with CDI, 1-6 and methyl 2-benzyl-3-aminopropionate (7-1) (Phytochemistry 1988, 27, 711-14) as described for 1-2 gave 7-2. R_f 0.34 (silica, 5% MeOH/CHCl₃).

¹H-NMR (300 MHz, CHCl₃) δ 1.0 (2H, m) 1.5 (9H, s), 2.6 (3H, m), 1.65 (2H, d), 2.6 (2H, t), 2.8 (1H, dd), 2.95-3.05 (2H, m) 3.40 (2H, m), 3.61 (3H, s), 3.40-3.65 (2H, m), 4.0 (2H, d), 6.75 (1H, t), 7.05 (1H, t), 7.10-7.30 (6H, m), 7.41 (1H, t), 7.78 (1H, d), 7.90 (1H, d), 8.12 (1H, s).

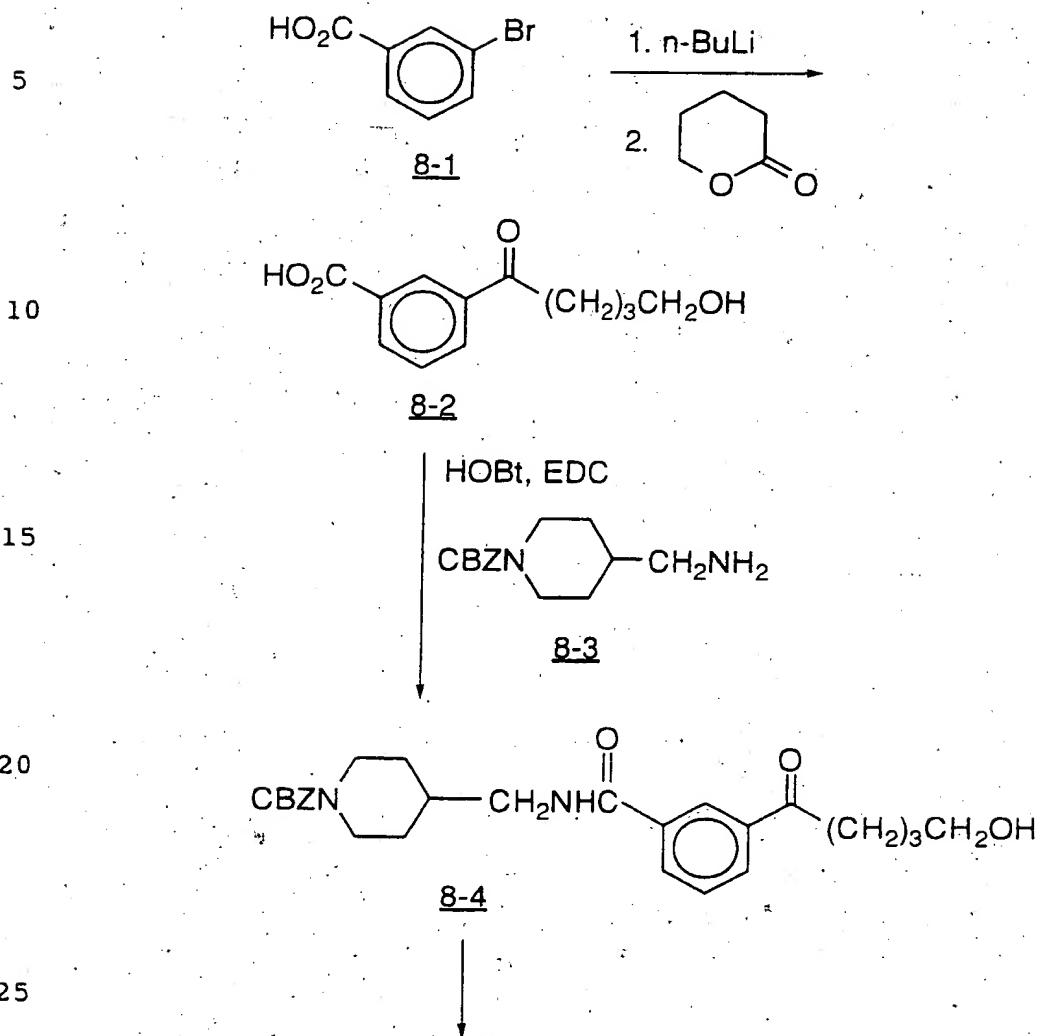
7-3

N-2-(4-Piperidylethyl)-N'-3-(2-benzylpropionic acid)-1,3-benzenedicarboxamide (7-3)

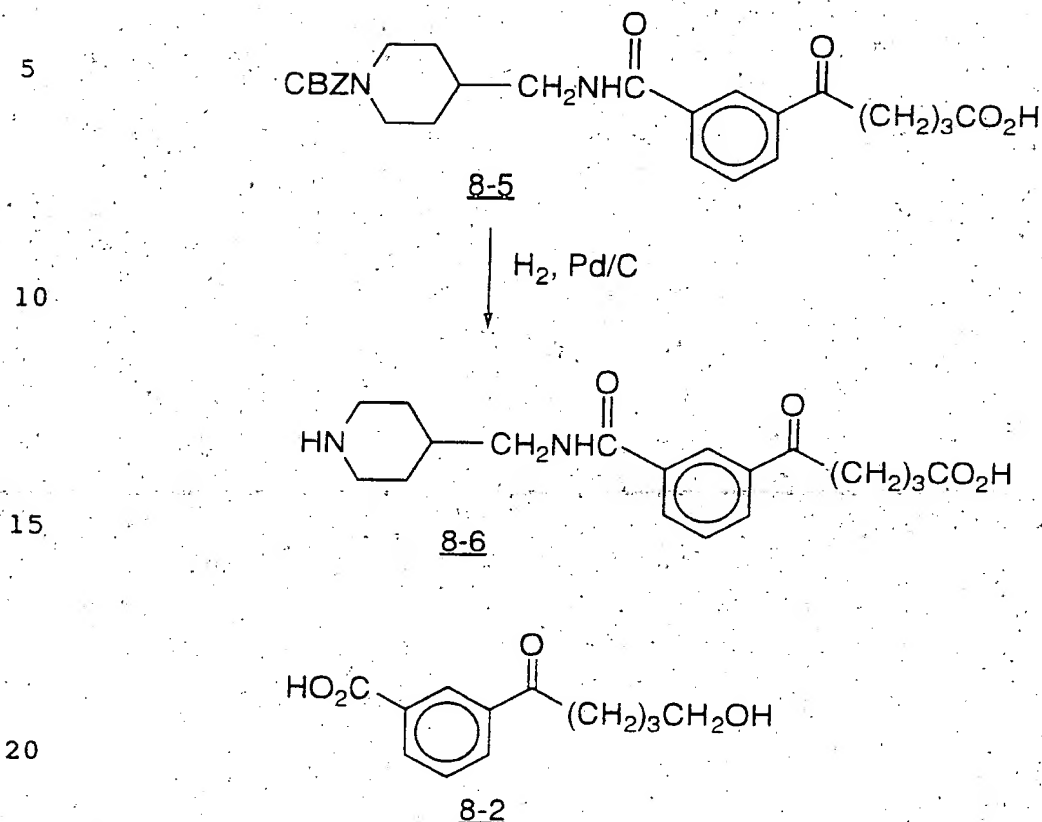
7-2 was hydrolyzed with LiOH·H₂O and then deprotected with HCl gas in EtOAc as described for 3-4 to provide pure 7-3. R_f 0.22 (silica, EtOH/H₂O/MeOH 9:1:1).

¹H NMR (300 MHz, D₂O + DCl) δ 1.2 (2H, m), 1.6-1.8 (3H, m), 2.0 (2H, d), 2.95 (4H, m), 3.20 (1H, m), 3.40 (4H, m), 3.60 (2H, m), 7.25 (5H, m), 7.60 (1H, t), 7.83 (1H, d), 7.88 (1H, d), 7.94 (1H, s).

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SCHEME 8

- 70 -

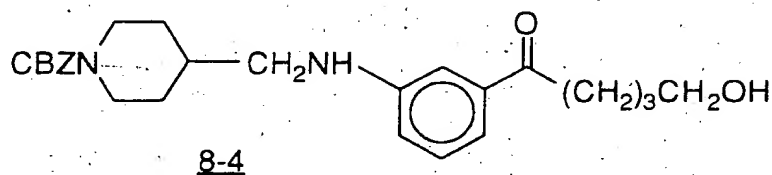
SCHEME 8 (CONT'D)3-(5-Hydroxypentanoyl)benzoic acid (8-2)

25 A solution of 3-bromobenzoic acid (Aldrich) (10.05 g, 0.05 moles) (8-1) in THF (250 ml) at -78° was treated with n-BuLi (0.1 moles) and the resulting solution was stirred at -78° for 1 hour. To this was added a solution of 8-valerolactone (Aldrich) (5.0 g, 0.05 moles) in THF (10 ml) at -78° and this was stirred at -78° for 3 hours and then

30 allowed to gradually warm to room temperature overnight. The reaction was quenched with enough 10% KHSO_4 solution to provide a pH 2-3 and then extracted with EtOAc. The organic extract was washed with brine, dried (Na_2SO_4) and the solvent was removed. The resulting residue was purified by flash chromatography on silica gel eluting with $\text{CHCl}_3/\text{MeOH}/\text{HOAc}$ 95:5:1 to give pure 8-2, R_f 0.3 (silica).

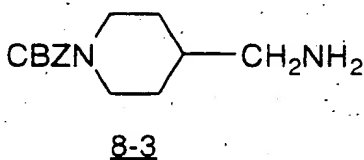
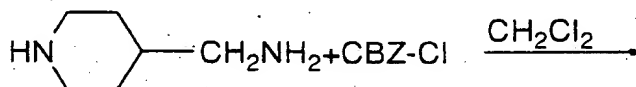
- 71 -

¹H NMR (300 MHz, CD₃OD) δ 1.65 (2H, m), 1.80 (2H, m), 3.10 (2H, t), 3.6 (2H, t), 7.61 (1H, t), 8.18 (2H, t), 8.50 (1H, m).



10 3-(5-Hydroxypentanoyl)-N-(N'-CBZ-4-piperidinylmethyl)benzene-carboxamide 8-4)

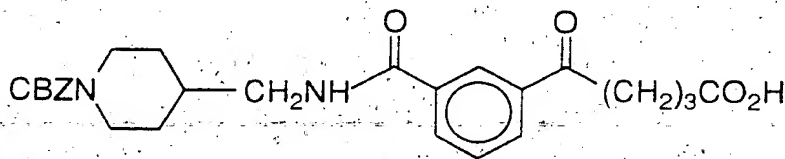
A solution of 8-2 (0.44 g, 2 mmoles) in DMF (25 ml) was treated with N-(CBZ-4-piperidinyl)methyl amine (0.53 g, 2 mmoles) (8-3), HOBT (0.3 g, 2.2 mmoles) EDC (0.44 g, 2.3 mmoles) followed by NMM (0.4 g, 4 mmoles) and the resulting solution was stirred for 16 hours. The solvent was removed and the residue was taken up in H₂O and extracted with EtOAc. The organic extract was washed with 10% KHSO₄ solution, brine, saturated NaHCO₃ solution, brine and dried (Na₂SO₄). Solvent removal gave a residue that was purified by flash chromatography on silica gel eluting with CHCl₃(97)/MeOH(3) to give pure 8-4. R_f 0.35 (silica, CHCl₃(95)/MeOH(5)).



N-CBZ-(4-Aminomethyl)piperidine

A solution of 4-(aminomethyl)piperidine (Aldrich) (5.0 g, 0.0438 mol) in CH_2Cl_2 (100 ml) was cooled to -78° and treated with CBZ-Cl (Aldrich) (0.022 mol) dropwise. The reaction mixture was stirred at -78° for 0.5 hours and then allowed to warm to 0° over 1 hour. The reaction mixture was filtered and the solution concentrated to give a residue that was purified by flash chromatography on silica gel eluting with 5% MeOH/ CHCl_3 , + 1% Et_3N to give pure product.

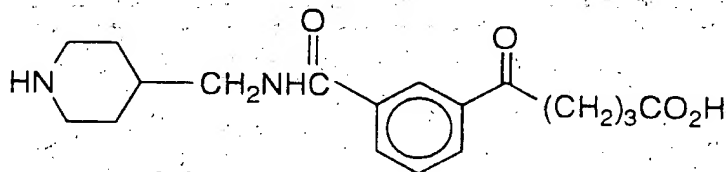
^1H NMR (300 MHz, CDCl_3) δ 1.1 (2H, m), 1.4 (3H, m), 1.7 (2H, bd), 2.57 (2H, d), 2.75 (2H, bt), 4.2 (2H, bs), 5.11 (2H, s), 7.2-7.4 (5H, m).



8-5

3-(4-Carboxybutanoyl)-N-(N'CBZ-4-piperidinylmethyl)benzene-carboxamide (8-5)

An acetone solution (15 ml) of 8-3 was treated with Jones reagent at -10° and the resulting orange-brown solution was stirred for 1 hour. The reaction mixture was diluted with H_2O and extracted with EtOAc. The organic extract was dried (Na_2SO_4), concentrated, and the resulting residue purified by flash chromatography on silica gel eluting with CHCl_3 (95)/MeOH(5)/HOAc(1), R_f 0.3.



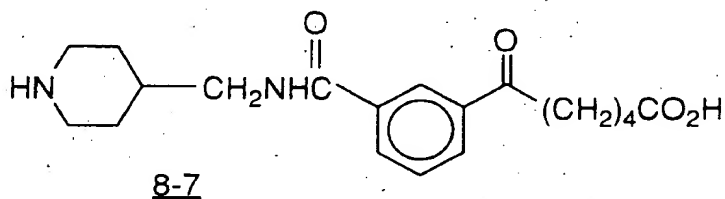
8-6

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3-(5-Carboxypentanoyl)-N-(4-piperidinylmethyl)-benzenecarboxamide
(8-6)

A solution of 8-5 (0.19 g) in MeOH (20 ml) was treated with 150 mg 10% Pd/C and this suspension was hydrogenated for 16 hours under balloon pressure. After the catalyst was removed by filtration, the solvent was removed and the residue purified by flash chromatography on silica gel eluting with EtOH(10)/conc. NH₄OH(1)/H₂O(1) to give pure 8-6.

¹H NMR (300 MHz, CD₃OD) δ 1.56 (4H, m), 1.82 (2H, m), 1.93 (3H, m), 2.20 (2H, m), 2.93 (2H, t), 3.40 (4H, m), 4.71 (1H, m), 7.45 (1H, t), 7.55 (1H, d), 7.70 (1H, d), 7.95 (1H, s).



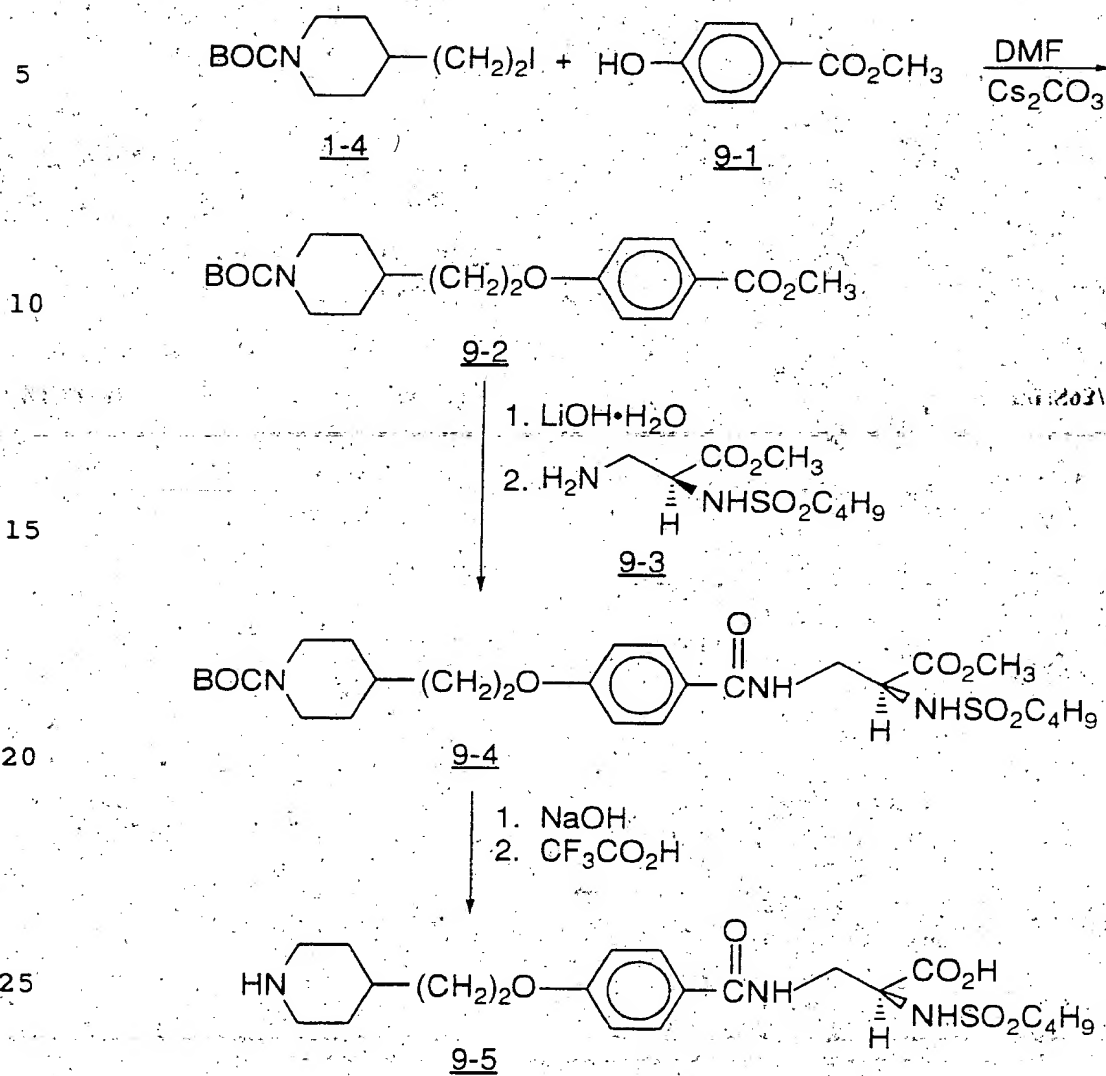
3-(5-Carboxypentanoyl)-N-(4-piperidinylmethyl)benzenecarboxamide
(8-7)

This compound was prepared as described for 8-6, wherein E-caprolactam (Aldrich) is used in the initial step, to provide 8-7 as a white solid.

¹H NMR (300 MHz, CD₃OD) δ 1.40-1.60 (2H, m), 1.60-1.85 (4H, m), 1.90-2.10 (3H, m), 2.35 (2H, t), 3.00 (2H, dt), 3.12 (2H, t), 3.33-3.5 (4H, m), 7.61 (1H, t), 8.06 (1H, d), 8.17 (1H, d), 8.43 (1H, s).

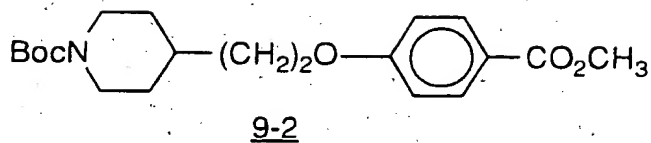
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SCHEME 9



30

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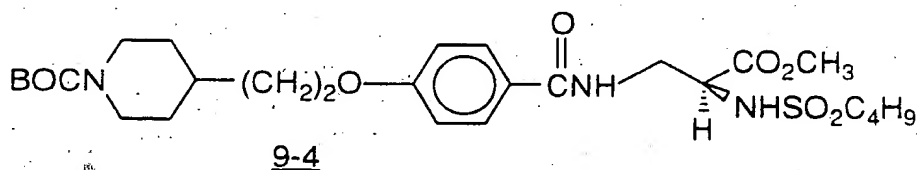
5

Methyl 4-[2-(N-BOC-4-Piperidiny)ethoxy]benzoate (9-2)

A solution of methyl 4-hydroxybenzoate (Aldrich) (0.4 g, 2.6 mmoles) 9-1 in DMF (10 ml) was treated with 2-(N-Boc-4-piperidiny)ethyl iodide 1-4 (0.6 g, 1.77 mmoles) and CS_2CO_3 (1.15 g, 3.5 mmoles) with stirring at room temperature for 48 hours. The reaction mixture was diluted with EtOAc, washed with H_2O , saturated NaHCO_3 , 10% KHSO_4 , brine dried (MgSO_4) and concentrated. The residue was purified by flash chromatography on silica gel eluting with 20% EtOAc/hexanes to give pure 9-2. R_f 0.3.

^1H NMR (300 MHz, CDCl_3) δ 1.36 (2H, m), 1.45 (9H, s), 2.44 (5H, m), 2.70 (2H, t), 3.88 (2H, s), 6.88 (2H, d), 7.96 (2H, d).

20



4-[2-(N-BOC-piperidin-4-yl)ethoxy]benzoyl-2(S)-n-butylsulfonylamino- β -alanine methyl ester (9-4)

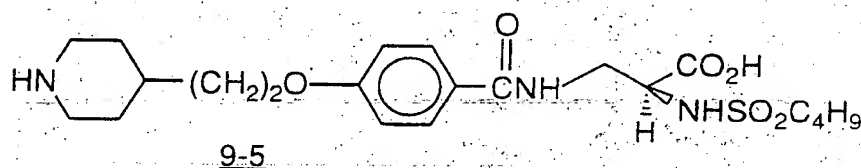
A solution of 9-2 (0.4 g, 1.14 mmoles) in H_2O (3 ml)/THF (4 ml) was treated with LiOH (2 mmoles) and the resulting solution stirred overnight at room temperature. The reaction mixture was acidified with 5% KHSO_4 extracted with EtOAc and the organic phase was washed with brine, dried (MgSO_4) and concentrated to give the desired acid. R_f 0.5 (silica, CHCl_3 (10)/MeOH (0.25)/AcOH (0.25).

This acid (0.1 g, 0.37 mmoles) was dissolved in CH_3CN (2 ml) and treated with methyl 3-amino-2(S)-n-butylsulfonylamino propionate (9-3) (0.1 g, 0.37 mmoles), BOP (0.246 g, 0.55 mmoles) and NMM (0.15 g, 1.48 mmoles) and the resulting mixture was stirred

- 76 -

overnight. Then, the reaction mixture was diluted with EtOAc, washed with H₂O, saturated NaHCO₃, 10% KHSO₄, brine, dried (MgSO₄) and concentrated. The residue was purified by flash chromatography on silica gel eluting with 60% EtOAc/hexanes to give pure 9-4. R_f 0.4 (silica, 60% EtOAc/hexanes).

¹H NMR (300 MHz, CDCl₃) δ 0.92 (3H, s), 1.20 (2H, m), 1.45 (9H, s), 1.67 (4H, m), 2.76 (2H, bt), 3.04 (2H, t), 3.80 (5H, m), 4.10 (4H, m), 4.31 (1H, m), 6.92 (2H, d), 7.79 (2H, d).



4-[2-(4-Piperidinyl)ethyloxy]-N-[3-(2(S)-n-butylsulfonylamino)-propionate]benzamide (9-5)

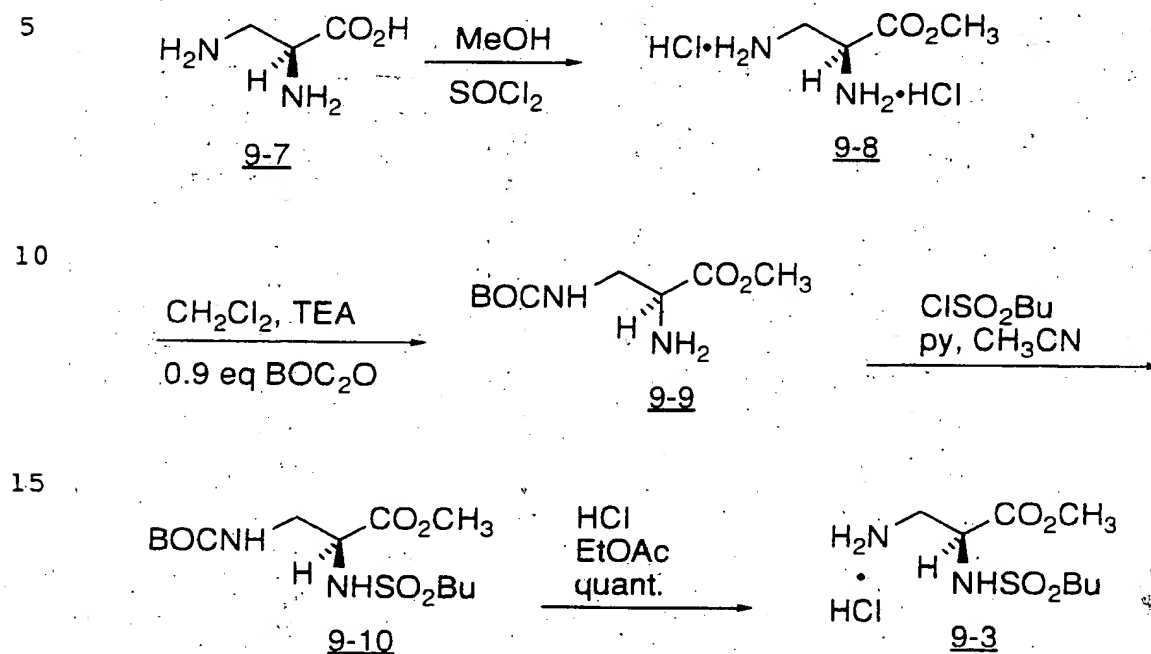
A solution of (9-4) (0.2 g, 0.37 mmoles) in EtOH (2 ml) was treated with NaOH (0.5 mmoles) and the resulting solution was stirred for 1 hour at room temperature. The reaction mixture was then acidified to pH 2-3 with 10% KHSO₄ solution and extracted with EtOAc. The organic extract was washed with brine, dried (MgSO₄) and concentrated to give the desired acid. R_f 0.25 (silica, CHCl₃(10)/MeOH(0.5)/AcOH(0.5)).

This acid (0.18 g, 0.34 mmoles) was dissolved in CH₂Cl₂ (2 ml) and treated at room temperature with CF₃CO₂H (2 ml) for 1 hour. The solvents were removed and the residue was purified by flash chromatography on silica gel eluting with EtOH(10)/H₂O(1)/NH₄OH(1) to give pure 9-5. R_f 0.5.

¹H NMR (300 MHz, D₂O) δ 0.68 (3H, s), 1.18 (2H, m), 1.40 (2H, m), 1.59 (2H, m), 1.73 (2H, m), 1.80 (2H, m), 1.94 (2H, bd), 2.92 (2H, dt), 3.06 (2H, t), 3.37 (2H, bd), 3.54 (1H, m), 3.81 (1H, dd), 4.12 (2H, t), 4.31 (1H, m), 7.02 (2H, d), 7.75 (2H, d).

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Preparation of Methyl 3-amino-2(S)-n-butylsulfonylaminopropionate
(9-3).



Methyl 2(S), 3-Diaminopropanoate (9-8)

Methanol (400 mL) was cooled to 0°C and thionyl chloride (217 mL, 3.0 moles, 20 eq) was added dropwise under argon. After addition was completed, the solution was warmed to room temperature for 20 minutes. 2(S), 3-Diaminopropanoic acid (Schweizerhall) (20 g, 0.243 mole) was crushed to a fine powder and added to the solution. The reaction was heated to reflux for 48 hours, at which time TLC showed a small amount of starting material remaining. An additional portion of methanol (100 mL) and thionyl chloride (72 mL) was prepared as before and added to the reaction at room temperature; the reaction was then stirred overnight at room temperature. The reaction was worked up by removal of solvent at 40°C in vacuo, to provide 9-8. R_f 0.72 (9:1:1 EtOH/H₂O/NH₄OH).

¹H NMR (400 MHz, D₂O) δ 4.55 (dd, J=5.4, 8.2 Hz, 1H), 3.92 (s, 3H), 3.64 (dd, J=8.2, 13.8 Hz, 1H), 3.55 (dd, J=5.4, 13.8 Hz, 1H).

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Methyl 2(S)-3(N-t-Butyloxycarbonyl)diaminopropanoate (9-9)

9-8 (6.0 g, 31.5 mmol) was crushed to a fine powder, suspended in 1L of CH₂Cl₂ and cooled to -78°C under argon.

5 Triethylamine (17.5 mL, 0.126 moles, 4 eq) was added dropwise; the solution gradually became homogenous. Di-t-butyldicarbonate (6.18 g, 2.83 mmol, 0.9 eq) was dissolved in 50 mL CH₂Cl₂ and added dropwise to the solution. After the addition was completed, the reaction was placed in an ice bath and stirred for 1-1/2 hours. The
10 reaction was transferred to a separatory funnel and extracted with 3 x 50 mL of 10% KHSO₄ solution. The aqueous layer was washed with 3 x 10 mL of CH₂Cl₂, then basified with saturated NaHCO₃ and 3N NaOH solution to pH 10 and extracted with 10 x 100 mL of CH₂Cl₂. The organic layer was dried with Na₂SO₄, filtered and evaporated to
15 give 4.9 g of a pale yellow oil. Column chromatography in 2.5% MeOH/EtOAc gave 9-9 as an oil. R_f 0.39 (5% MeOH/EtOAc). ¹H NMR (400 MHz, CDCl₃) δ 5.0 (bs, 1H), 3.72 (s, 3H), 3.56 (t, J=5.7 Hz, 1H), 3.46 (m, 1H), 3.23 (m, 1H), 1.55 (bs, 2H), 1.42 (s, 9H).

Methyl 2(S)-(N-Butylsulfonylamino)-3-(N-t-butyloxycarbonylamino)-diaminopropionic (9-10)

9-9 was dissolved in acetonitrile (100 mL) and three portions of n-butylsulfonyl chloride (1.62 mL, 12.5 mmol), and
25 pyridine (1.0 mL, 12.5 mmol) were added over a period of three hours. The reaction was allowed to stir overnight, concentrated to 1/4 its original volume, then diluted with 100 mL EtOAc and washed with 10% KHSO₄ (5 x 20 mL), dried with brine and MgSO₄, filtered and evaporated. Column chromatography in 20%-40% EtOAc/hexanes gave
30 9-10 as an oil. R_f 0.6 (5% MeOH/CHCl₃).

¹H NMR (400 MHz, CDCl₃) δ 5.48 (bd, 1H), 4.9 (bs, 2H), 4.22 (m, 1H), 3.8 (s, 3H), 3.53 (m, 2H), 3.02 (m, 2H), 1.80 (m, 2H), 1.46 (m, 2H), 1.43 (s, 9H), 0.94 (t, J=7.4 Hz, 3H).

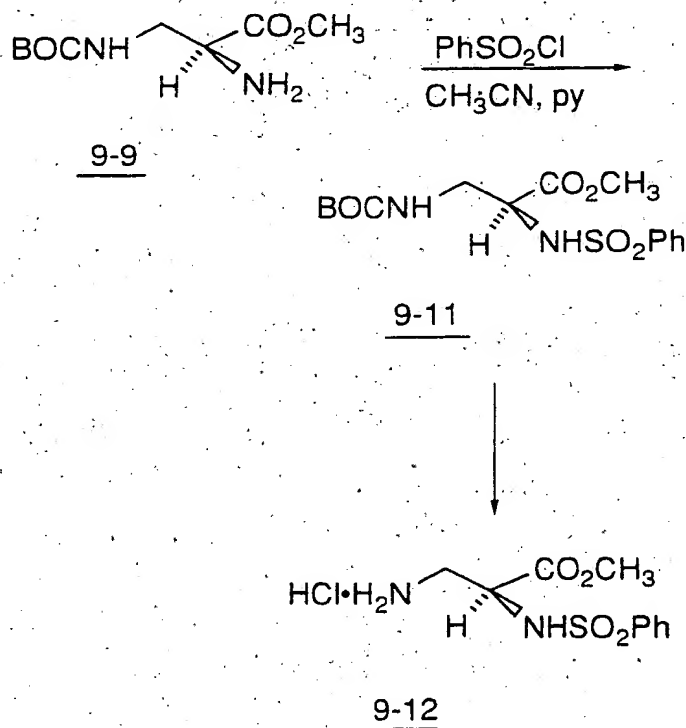
- 79 -

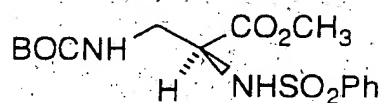
2(S)-(N-Butylsulfonylamino)-3-aminopropionic acid methyl ester hydrochloride (9-3)

9-10 (2.0 g, 5.9 mmol) was dissolved in 30 mL of EtOAc and cooled to -40°C. HCl gas was bubbled through the solution until it was saturated, then the reaction was warmed to 0°C and stirred for 1 hour. The excess HCl was removed under vacuum at room temperature and the reaction was concentrated at 35°C to give 9-3. R_f 0.6 (9:1 EtOH/H₂O).

¹H NMR (400 MHz, CDCl₃) δ .1 (bs, 2H), 7.2 (m, 1H), 4.65 (m, 1H), 3.82 (s, 3H), 3.65 (m, 1H), 3.54 (m, 1H), 3.20 (bs, 2H), 1.8 (m, 2H), 1.45 (m, 2H), 0.95 (t, J=7.3 Hz).

Preparation of Methyl 2(S)-Phenylsulfonylamino-3-aminopropionate hydrochloride (9-12)



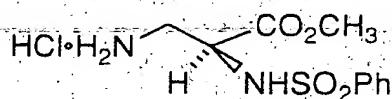


9-11

2(S)-(Phenylsulfonylamino)-3-(N-t-butyloxycarbonylamino)propionic acid methyl ester (9-11)

Utilizing the procedure for converting 9-9 to 9-10, 9-9 (700 mg, 3.1 mmol) gave 9-11 (900 mg) as a white solid after flash chromatography (silica, 30% EtOAc/hexanes).

¹H NMR (400 MHz, CDCl₃) δ 7.85 (m, 2H), 7.60-7.50 (m, 3H), 5.67 (m, 1H), 4.00 (m, 1H), 3.56 (s, 3H), 3.47 (m, 2H), 1.45 (s, 9H).

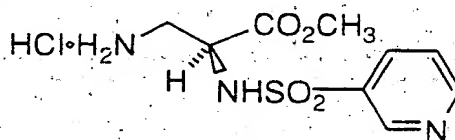


9-12

Methyl 2(S)-(Phenylsulfonylamino)-3-aminopropionate Hydrochloride (9-12)

Utilizing the procedure for converting 9-10 to 9-3, 9-11 (900 mg) gave 9-12 (800 mg) as a white solid.

¹H NMR (400 MHz, CD₃OD) δ 7.88 (m, 2H), 7.65 (m, 1H), 7.60 (m, 1H), 4.25 (m, 1H), 3.42 (s, 3H), 3.35 (m, 1H), 3.10 (m, 1H).



9-13

Methyl 2(S)-(3-Pyridylsulfonylamino)-3-aminopropionate hydrochloride (9-13)

Compound 9-13 was prepared in a manner similar to that used for 9-12, utilizing 3-chlorosulfonylpyridine (Synthesis, 1983, p.

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822). R_f 0.34 (9:1:1 EtOH/H₂O/NH₄OH) δ 9.3 (s, 1H), 9.0 (dd, J = 1.5 Hz, 1H), 8.9 (d, J = 9Hz, 1H), 8.2 (dd, J = 5, 9Hz, 1H), 4.6 (dd, J = 5, 9Hz, 1H), 3.6 (s, 3H), 3.5 (dd, J = 5, 13Hz, 1H), 3.3 (dd, J = 9, 13 Hz, 1H).

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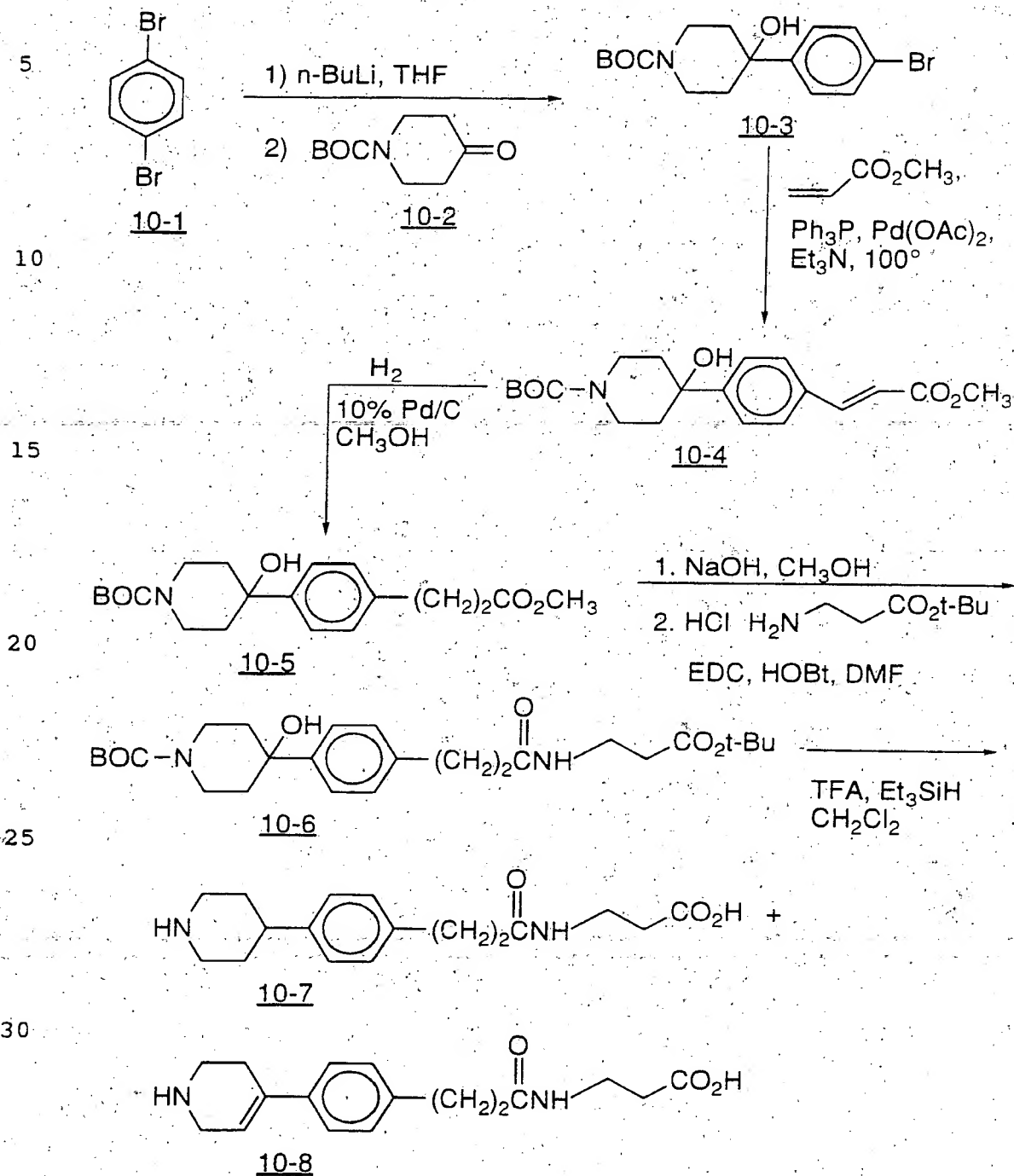
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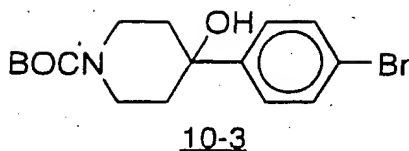
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SCHEME 10



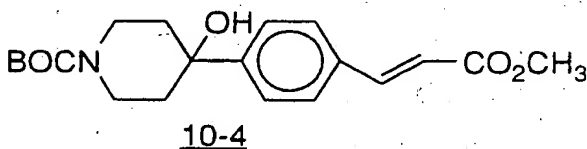
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4-(N-BOC-4-Hydroxypiperidin-4-yl)bromobenzene (10-3)

A solution of 1,4-dibromobenzene (7.10 g, 30.1 mmol) in THF (50 ml) at -78° was treated with n-BuLi (18.7 ml, 30 mmol, 1.6 M/hexane) and after 1.0 hour stirring at -78° , N-BOC-4-piperidone (10-2) (2.0 g, 10.04 mmol) in THF (2 ml) was added. After 1 hour the cooling bath was removed and the reaction mixture was stirred for 2 hours. The reaction mixture was then diluted with EtOAc, washed with water, 10% KHSO₄, brine, dried (MgSO₄) and concentrated. The residue was purified by flash chromatography on silica gel eluting with 20% EtOAc/hexanes to give pure 10-3, R_f 0.15 (silica, 20% EtOAc/hexanes).

¹H NMR (300 MHz, CDCl₃) δ 1.45 (9H, s), 1.67 (2H, bs), 1.90 (2H, m), 3.16 (2H, dt), 3.97 (2H, bd), 7.30 (2H, d), 7.43 (2H, d).



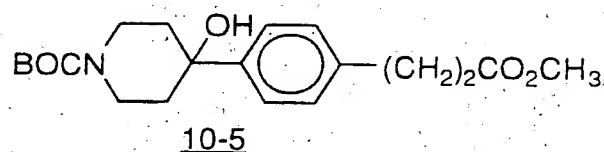
Methyl 3-[4-(N-BOC-4-Hydroxypiperidin-4-yl)phenyl]acrylate (10-4)

A solution of 10-3 (0.5 g, 1.4 mmol), methyl acrylate (1.2 g, 14 mmol), Pd(OAc)₂ (0.031 g, 0.24 mmol), Et₃N (0.56 g, 5.6 mmol) and Ph₃P (0.17 g, 0.56 mmol) in CH₃CN (40 ml) was heated at 100° in a sealed tube for 24 hours.

The cooled reaction mixture was diluted with EtOAc, washed with H₂O, 10% KHSO₄, brine, dried (MgSO₄) and concentrated. The residue was purified by flash chromatography on

- 84 -

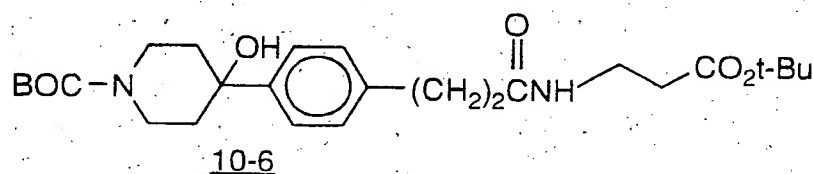
silica gel eluting with 25% EtOAc/hexanes to give pure 10-4. R_f 0.55 (silica, 50% EtOAc/hexanes).



10 Methyl 3-[4-(N-BOC-4-Hydroxypiperidin-4-yl)phenyl]propionate (10-5)

A solution of 10-4 (0.42 g, 1.16 mmoles) in MeOH (6 ml) was treated with 0.17 g 10% Pd/C and this was hydrogenated under 1 atm. of H₂ pressure for 48 hours. Solvent removal and purification by flash chromatography on silica gel eluting with 50% EtOAc/hexanes gave pure 10-5. R_f 0.55 (silica, 50% EtOAc/hexanes).

¹H NMR (300 MHz, CDCl₃) δ 1.45 (9H, s), 1.62 (2H, m), 1.72 (2H, bd), 1.97 (2H, m), 2.64 (2H, t), 2.95 (2H, t), 3.24 (2H, by), 4.03 (2H, m), 7.21 (2H, d), 7.40 (2H, d).



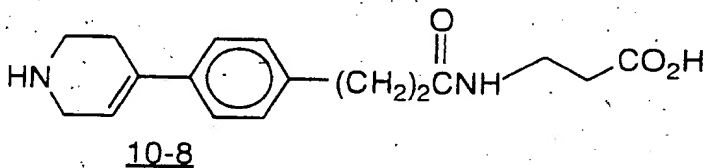
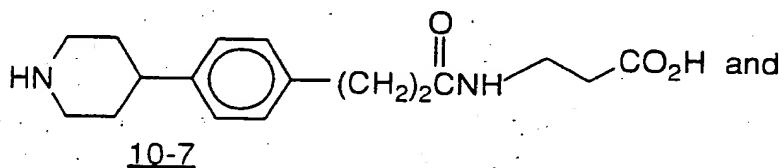
30 4-(N-BOC-4-Hydroxypiperidin-4-yl)phenyl-3-propionyl-β-alanine t-butyl ester (10-6)

A solution of 10-5 (0.4 g, 1.1 mmoles) in CH₃OH (6 ml) was treated at room temperature with 1N NaOH (4.4 ml) and the resulting solution was stirred for 1 hour. The solvent was removed, the residue acidified with 10% KHSO₄ and extracted with EtOAc. The organic extract was dried (MgSO₄) and concentrated to give the desired acid (10-9) as a white solid. R_f 0.75 (silica, CH₂Cl₂/AcOH (0.51/

- 85 -

MeOH(0.50).

A solution of this acid (0.275 g, 0.79 mmoles) in DMF (5 ml) at -15° was treated with β -alanine hydrochloride t-butyl ester (0.16 g, 0.94 mmoles), HOBT (0.12 g, 0.94 mmoles), DIPEA (0.6 ml, 3.1 mmoles) followed by EDC (0.18 g, 0.94 mmoles). The cooling bath was then removed and the reaction mixture stirred at ambient temperature for 18 hours. The reaction mixture was diluted with EtOAc (50 ml), washed with H₂O, saturated NaHCO₃, 10% KHSO₄, brine, dried (MgSO₄) and concentrated. The residue was purified by flash chromatography on silica gel eluting with 80% EtOAc/hexanes to give pure 10-6. R_f 0.25 (silica, 80% EtOAc/hexanes). ¹H NMR (300 MHz, CDCl₃) δ 1.45 (9H, s), 1.50 (9H, s), 1.75 (2H, bd), 2.00 (2H, m), 2.38 (2H, t), 2.46 (2H, t), 2.96 (2H, t), 3.26 (2H, t), 3.46 (2H, q), 4.04 (2H, bd), 7.22 (2H, d), 7.40 (2H, d).



4-(Piperidin-4-yl)phenyl-3-propionyl- β -alanine (10-7) 4-(1,2,5,6-Tetrahydropyridin-4-yl)phenyl-3-propionyl- β -alanine (10-8)

A solution of 10-6 (0.225 g, 0.47 mmoles) in CH₂Cl₂ (5 ml) was treated with Et₃SiH (0.33 g, 4.2 mmoles) at ambient temperature and the resulting solution was stirred for 18 hours. The solvent was removed and the residue was purified by flash chromatography on silica gel eluting with EtOH(10)/H₂O(1)/NH₄OH(1) to give two components: 10-8 had R_f 0.25 under these conditions:

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¹H NMR (300 MHz, D₂O) δ 2.48 (2H, t), 2.87 (2H, t), 3.13 (2H, b), 3.25 (2H, t), 3.56 (2H, t), 3.72 (2H, t), 4.20 (2H, bs), 6.49 (1H, m), 7.59 (2H, d), 7.78 (2H, d).

5 10-7 had R_f 0.2 (silica, EtOH(10)/H₂O(1)/NH₄OH(1) and
¹H NMR (300 MHz, D₂O) δ 1.87 (2H, m), 2.10 (4H, m), 2.50 (2H, t), 2.88 (2H, t), 3.12 (2H, dt), 3.20 (2H, t), 3.5 (2H, m), 7.41 (2H, d), 7.48 (2H, d).

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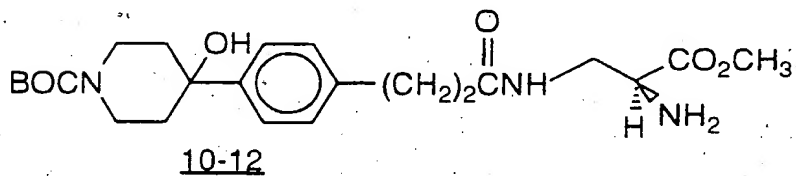
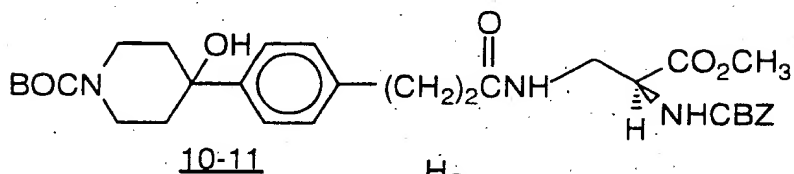
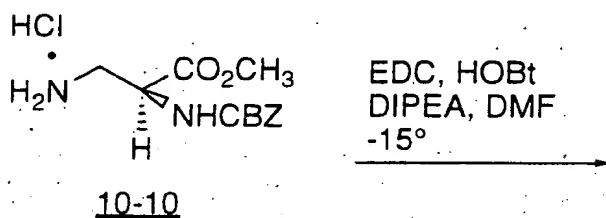
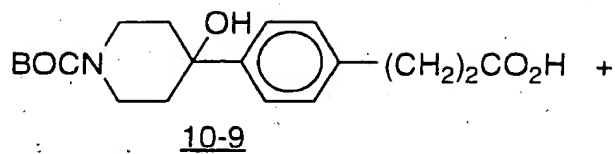
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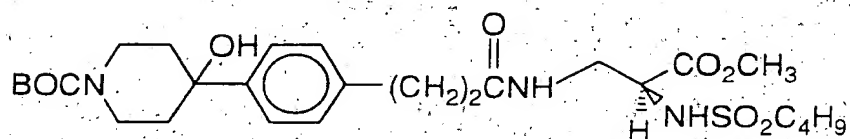
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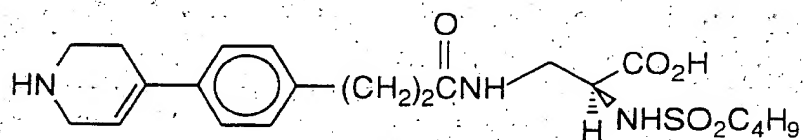
- 88 -

10-12

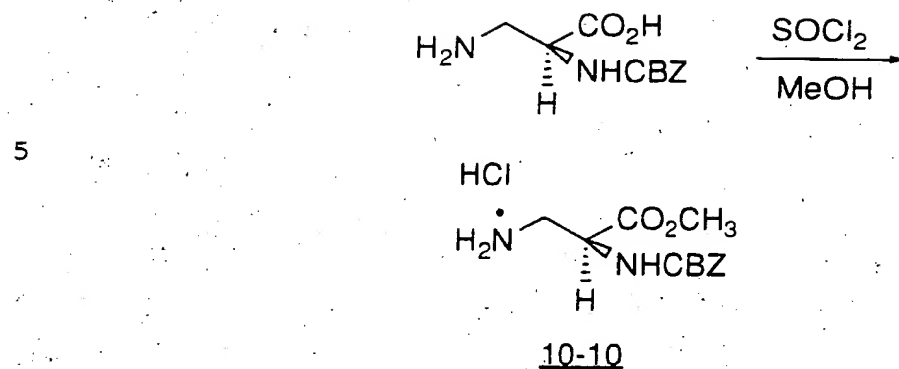
$\text{ClSO}_2\text{C}_4\text{H}_9$
 CH_2Cl_2 , Et_3N
 -15°



1. LiOH H_2O
2. $\text{CF}_3\text{CO}_2\text{H}$



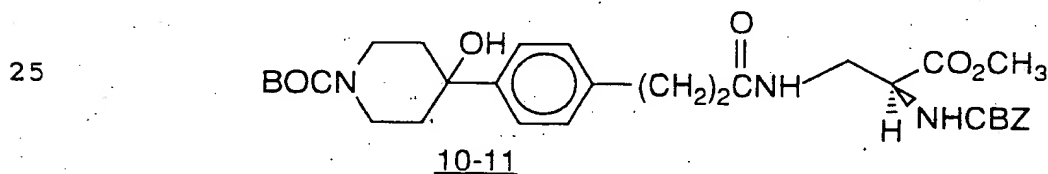
- 89 -



Methyl 3-amino-2(S)-benzyloxycarbonylaminopropionate hydrochloride
(10-10)

15 3-Amino-2(S)-benzyloxycarbonylaminopropionic acid (Fluka) (5.0 g, 21.0 mmoles) was suspended in MeOH and at -10° SOCl_2 (23.0 mmoles) was added. The reaction mixture was allowed to gradually warm to room temperature over 16 hours. The solvent was then removed and the resulting solid was triturated with Et_2O to give 10-10.

20 ^1H NMR (300 MHz, D_2O) δ 3.32 (2H, m), 3.52 (2H, m), 3.70 (1H, m), 3.80 (4H, m), 4.59 (1H, m), 5.18 (3H, s), 7.45 (5H, s).



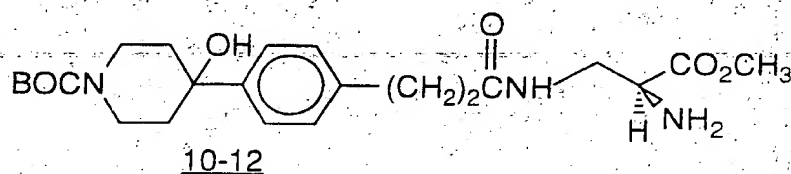
30 4-(N-BOC-4-Hydroxypiperidin-4-yl)phenyl-3-propionyl-[2(S)-benzyloxycarbonylaminol]- β -alanine methyl ester (10-11)

A solution of 10-9 (0.36 g, 1.3 mmoles) in DMF (5 ml) was treated with methyl 3-amino-2(S)-benzyloxycarbonylaminopropionate (10-10) (0.34 g, 1.56 mmoles), HOBt (0.16 g, 1.56 mmoles), DIPEA (0.5 g, 4.12 mmoles) and after cooling to -15° , EDC

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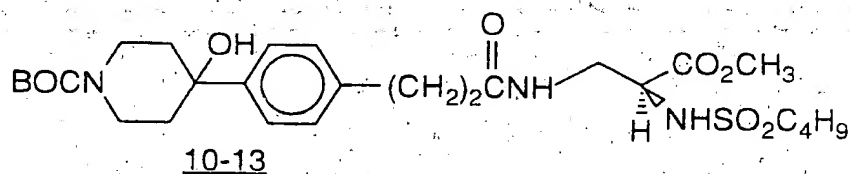
(0.24 g, 1.24 mmoles) was added. The cooling bath was then removed and the reaction mixture was stirred for 18 hours. The reaction mixture was diluted with EtOAc (50 ml), washed with H₂O, saturated NaHCO₃, 10% KHSO₄, brine, dried (MgSO₄) and concentrated. The residue was purified by flash chromatography on silica gel eluting with 90% EtOAc/hexanes to give pure 10-11, R_f 0.35.

¹H NMR (300 MHz, CDCl₃) δ 1.47 (9H, s), 1.63 (2H, m), 1.94 (2H, m), 2.44 (2H, m), 2.91 (2H, t), 3.23 (2H, bt), 3.61 (2H, m), 3.73 (3H, m), 4.00 (2H, bd), 4.29 (1H, m), 5.10 (2H, s), 7.16 (2H, m), 7.37 (7H, m).



4-(N-BOC-4-Hydroxypiperidin-4-yl)phenyl-3-propionyl-[2(S)-amino]-β-alanine methyl ester (10-12)

A solution of 10-11 (0.4 g, 0.7 mmoles) in MeOH (4 ml) was treated with 10% Pd/C (0.16 g) and then hydrogenated at 1 atmosphere for 1 hour. The catalyst was removed and the reaction mixture was concentrated to give 10-12 as a white solid. R_f 0.35 (silica, 20% CH₃OH/EtOAc).

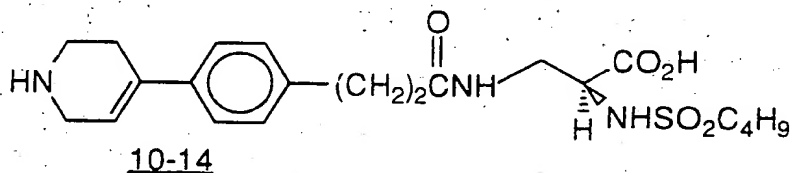


4-(N-BOC-4-Hydroxypiperidin-4-yl)phenyl-3-propionyl-[2(S)-n-butylsulfonylamino]-β-alanine methyl ester (10-13)

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A solution of 10-12 (0.3 g, 0.7 mmoles) in CH_2Cl_2 (5 ml) was treated at 0°C with Et_3N (0.14 g, 1.4 mmoles) followed by n-butylsulfonyl chloride (0.22 g, 1.4 mmoles) and the resulting mixture was stirred for 1.0 hours. The reaction mixture was then diluted with EtOAc, washed with H_2O , saturated NaHCO_3 , 10% KHSO_4 , brine dried (MgSO_4) and concentrated. The residue was purified by flash chromatography on silica gel eluting with 60% EtOAc/hexanes to give pure 10-13, R_f 0.2 (silica, 60% EtOAc/hexanes).

^1H NMR (300 MHz, CDCl_3), δ 0.95 (3H, t), 1.48 (9H, s), 1.59 (3H, m), 1.73 (2H, m), 1.95 (2H, m), 2.50 (2H, t), 2.94 (2H, m), 3.24 (2H, dt), 3.57 (2H, m), 3.79 (3H, s), 4.02 (2H, m), 7.22 (2H, d), 7.43 (2H, d).

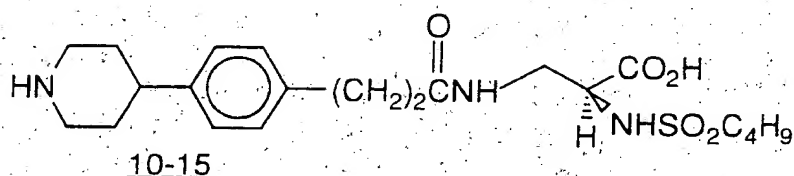


4-(1,2,5,6-Tetrahydropyridin-4-yl)phenyl-3-propionyl-[2(S)-n-butylsulfonylamino]- β -alanine (10-14)

A solution of 10-13 (0.2 g; 0.36 mmoles) in CH_3OH (2 ml) was treated with LiOH (1.0 mmoles) at room temperature with stirring for 4 hours. The solvent was removed, the residue acidified with 10% KHSO_4 and this was extracted with EtOAc. The organic extract was washed with brine, dried (MgSO_4), and concentrated to give the desired acid. R_f 0.25 (silica, CH_2Cl_2 (10)/ MeOH (0.5)/ AcOH (0.5)).

This acid (0.18 g, 0.33 mmoles) was dissolved in CH_2Cl_2 (2 ml) and treated with $\text{CF}_3\text{CO}_2\text{H}$ (2 ml) at room temperature with stirring for 1 hour. The solvent was removed and the residue was purified by flash chromatography on silica gel eluting with EtOH(10)/ NH_4OH (1)/ H_2O (1) to give pure 10-14.

^1H NMR (300 MHz, D_2O) δ 0.75 (3H, t), 1.26 (2H, m), 1.54 (2H, m), 2.45 (2H, m), 2.64 (2H, bs), 2.78 (2H, m), 2.92 (2H, m), 3.35 (4H, m), 3.70 (2H, m), 3.91 (1H, m), 6.00 (1H, m), 7.12 (2H, d), 7.30 (2H, d).

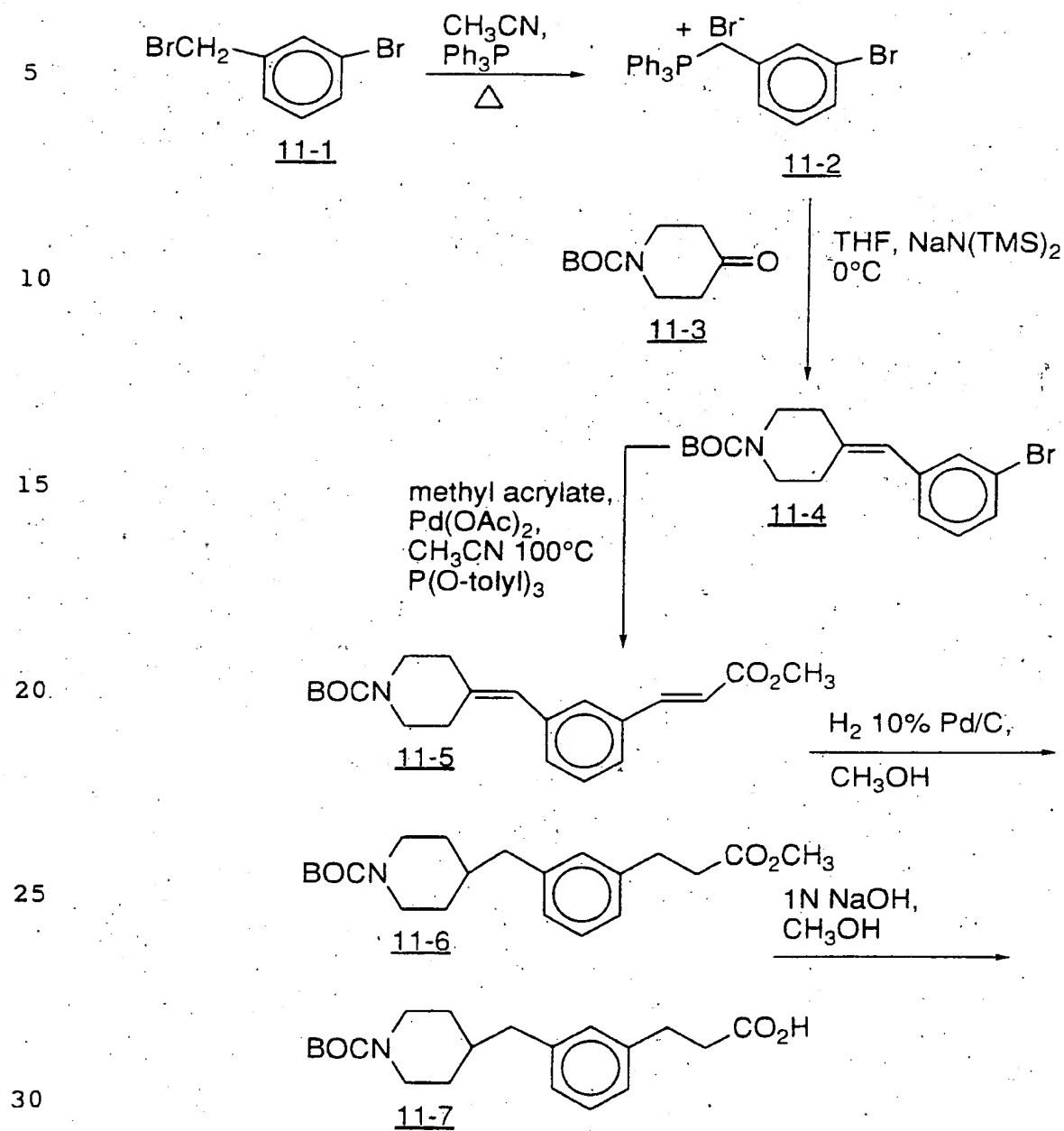


4-(Piperidin-4-yl)phenyl-3-propionyl-[2(S)-n-butyl-sulfonylamino]-β-alanine (10-15)

A solution of 10-14 (0.05 g, 0.114 mmoles) in CH₃OH (1 ml) was treated with 10% Pd/C (25 mg) and then hydrogenated for 2 hours at 1 atm H₂. The catalyst was then removed by filtration. The solution concentrated to give pure 10-15. R_f 0.3 (silica, EtOH(10)/H₂O(1)/NH₄OH(1)).

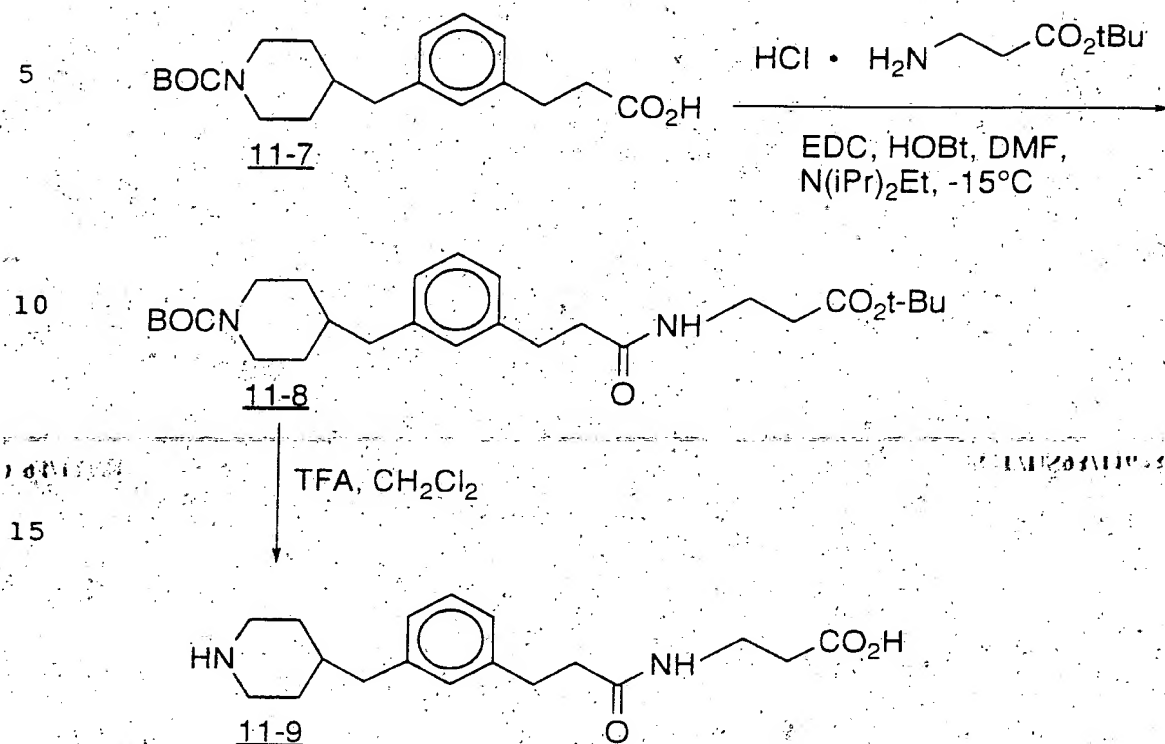
¹H NMR (300 MHz, CD₃OD) δ 0.86 (3H, t), 1.35 (2H, m), 1.68 (2H, m), 1.80 (2H, m), 1.96 (2H, bd), 2.40 (2H, m), 2.79 (3H, m), 2.97 (2H, m), 3.02 (2H, dt), 3.40 (2H, bd), 3.52 (2H, m), 4.06 (1H, m), 7.08 (5H, s).

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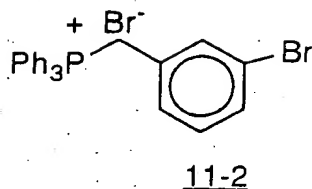
SCHEME 11

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SCHEME 11 (CONT'D)



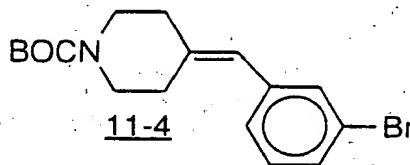
- 95 -



3-Bromobenzyltriphenylphosphonium bromide (11-2)

A stirred mixture of 3-bromobenzyl bromide (Aldrich) (5.1 g, 20.5 mmoles), triphenylphosphine (54 g, 0.20 moles), and CH₃CN (100 mL) was refluxed for 20 hours. The cooled reaction mixture was then concentrated and the residue triturated with hexanes (10x) to remove excess triphenylphosphine. The remaining white solid was collected by filtration and then dried in vacuo to give 11-2 as a white solid.

¹H NMR (300 MHz, CDCl₃) δ 7.90-7.60 (m, 15H), 7.28 (m, 2H), 7.06 (t, J=8 Hz, 1H), 6.97 (m, 1H), 5.60 (d, J= 15Hz, 2H).



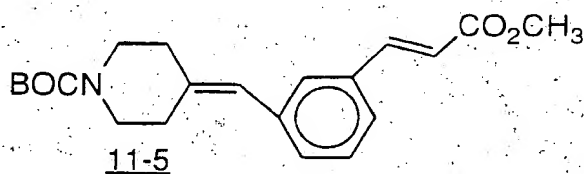
3-[(N-Boc-(1,2,3,5,6-pentahydropyridin-4-yl)methylene)-bromobenzene (11-4)

To a stirred solution of 11-2 (5.1 g, 10.0 mmoles) in THF (50 mL) at 0°C was added NaN(TMS)₂ (13.0 mL), 13.0 mmoles, 1M/hexanes) dropwise. After 15 minutes the orange mixture was treated with 11-3 (2.0 g, 10.0 mmoles) in THF(10 mL), followed by removal of the cooling bath. After 20 hours the reaction mixture was diluted with EtOAc and then washed with H₂O, saturated NaHCO₃, 5% KHSO₄, and brine, dried (MgSO₄) and concentrated. Flash

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chromatography (silica, 5% EtOAc/hexanes) gave 11-4 as a colorless oil. R_f 0.49 (silica, 5% EtOAc/hexanes).

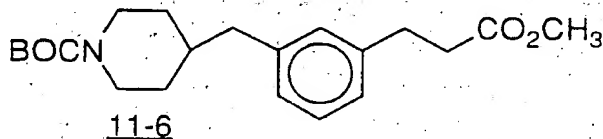
1H NMR (300 MHz, $CDCl_3$) δ 7.40-7.10 (m, 4H), 6.29 (s, 1H), 3.50 (m, 2H), 3.40 (m, 2H), 2.42 (m, 2H), 2.32 (m, 2H), 1.47 (s, 9H).



Methyl 3-[3-(N-BOC-1,2,3,5,6-Pentahydropyridin-4-yl-methylene)-phenyl]acrylate (11-5)

A mixture of 11-4 (400 mg, 1.1 mmol), methyl acrylate (1.0 g, 1.0 mL, 10.0 mmol), $Pd(OAc)_2$ (26 mg, 0.11 mmol), NEt_3 (0.16 mL, 1.1 mmol), tri-*o*-toluyl-phosphine (0.14 g, 0.45 mmol), and CH_3CN (6 mL) was heated at $100^\circ C$ in sealed tube. After 24 hour the cooled reaction mixture was diluted with EtOAc and then washed H_2O , saturated $NaHCO_3$, 5% $KHSO_4$, and brine, dried ($MgSO_4$), and concentrated. Flash chromatography (silica, 5% EtOAc/hexanes) gave 11-5 as yellow solid. R_f = 0.30 (silica, 5% EtOAc/hexanes).

1H NMR (300 MHz, $CDCl_3$) δ 7.70 (d, J =17 Hz, 1H), 7.40-7.20 (m, 4H), 6.42 (d, J =17 Hz, 1H), 6.37 (s, 1H), 3.53 (m, 2H), 3.38 (m, 2H), 2.43 (m, 2H), 2.35 (m, 2H), 1.48 (s, 9H).



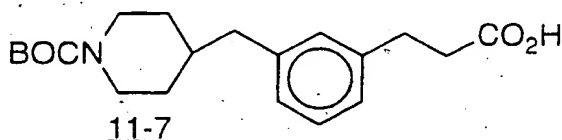
Methyl 3-[3-(N-BOC-Piperidin-4-ylmethyl)phenyl]propionate (11-6)

A mixture of 11-5 (310 mg, 0.87 mmol), 10% Pd/C (125 mg), and CH_3OH (6 mL) was stirred under hydrogen atmosphere (1 atm) at ambient temperature. After 20 hours the reaction mixture was

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filtered through a celite pad and the filtrate concentrated to give 11-6 as a yellow oil. R_f 0.30 (silica, 10% EtOAc/hexanes).

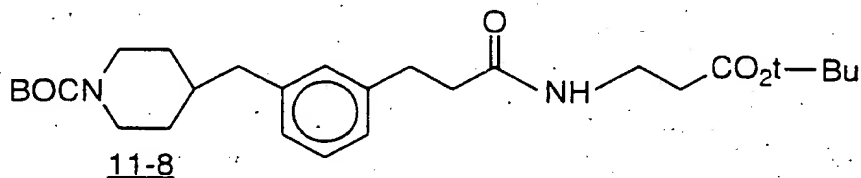
1H NMR (300 MHz, $CDCl_3$) δ 7.21 (m, 2H), 7.02 (m, 2H), 4.10 (m, 2H), 3.88 (s, 3H), 2.95 (m, 2H), 2.64 (m, 4H), 2.53 (d, $J=7$ Hz, 2H), 1.65 (m, 2H), 1.47 (s, 9H), 1.15 (m, 2H).



3-[3-(N-BOC-piperidin-4-ylmethyl)phenyl]propionic acid (11-7)

A solution of 11-6 (290 mg, 0.80 mmoles), 1N NaOH (3 mL), and CH_3OH (4 mL) was stirred at ambient temperature for 1.0 hour. The reaction was then acidified with 10% $KHSO_4$ and extracted with EtOAc. The EtOAc portion was then washed with brine, dried ($MgSO_4$), and concentrated to give 11-7 as a yellow oil. R_f 0.58 (silica, 10:0.5:0.5 $CH_2Cl_2/CH_3OH/HOAc$).

1H NMR (300 MHz, $CDCl_3$) δ 7.22 (m, 2H), 7.01 (m, 2H), 4.07 (m, 2H), 2.94 (m, 2H), 2.68 (m, 2H), 2.65 (m, 2H), 2.52 (d, $J=7$ Hz, 2H), 1.62 (m, 2H), 1.47 (s, 9H), 1.14 (m, 2H).

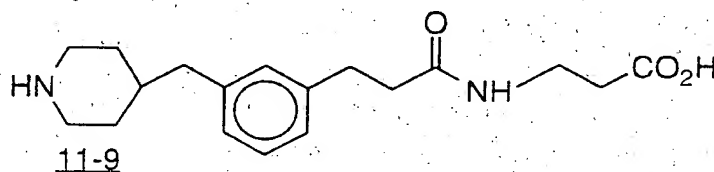


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3-[3-(N-BOC-piperidin-4-ylmethyl)phenyl]propionyl- β -alanine-tert-butyl ester (11-8)

To a stirred solution of 11-7 (275 mg, 0.79 mmol), HOBT (130 mg, 0.95 mmol), N(i-Pr)₂Et (0.55 mL, 3.2 mmol), tert-butyl- β -alanine hydrochloride (160 mg, 0.95 mmol), and DMF (4 mL), at -15°C was added EDC (183 mg, 0.95 mmol) followed by removal of the cooling bath. After 20 hours the reaction mixture was diluted with EtOAc and then washed with H₂O, saturated NaHCO₃, 10% KHSO₄, and brine, dried (MgSO₄), and concentrated. Flash chromatography (silica, 50% EtOAc/hexanes) gave 11-8 as a colorless oil. R_f 0.21 (silica, 50% EtOAc/hexanes).

¹H NMR (300 MHz, CDCl₃) δ 7.22 (m, 2H), 7.00 (m, 3H), 6.04 (m, 1H), 4.10 (m, 2H), 3.48 (m, 2H), 2.96 (m, 2H), 2.66 (m, 2H), 2.51 (m, 2H), 2.43 (m, 2H), 1.63 (m, 2H), 1.48 (s, 18H), 1.16 (m, 2H).

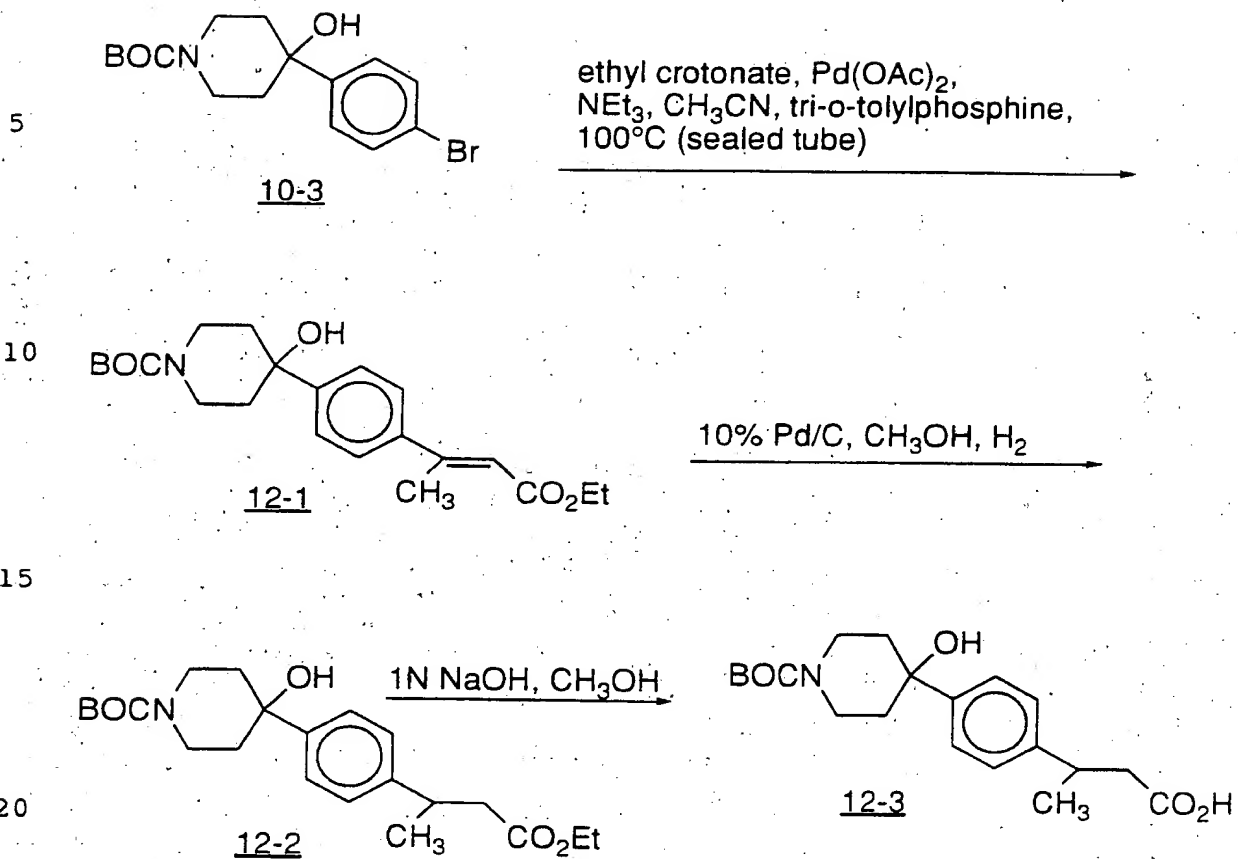


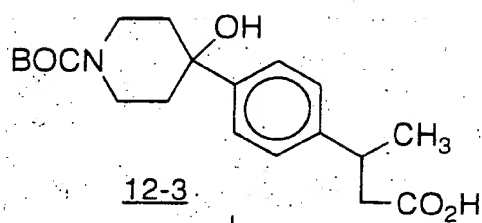
3-[3-(Piperidin-4-ylmethyl)phenyl]propionyl- β -alanine (11-9)

A solution of 11-8 (225 mg, 0.48 mmol), TFA (2.5 mL), and CH₂Cl₂ (2.5 mL) was stirred at ambient temperature for 1.0 h. Concentration followed by flash chromatography (silica, 10:1:1 ethanol/H₂O/NH₄OH) gave 11-9 as a white solid. R_f 0.44 (silica, 10:1:1 ethanol/H₂O/NH₄OH).

¹H NMR (400 MHz, D₂O) δ 7.40-7.00 (m, 4H), 3.38 (m, 2H), 3.21 (m, 2H), 2.90 (m, 2H), 2.60 (d, J=7Hz, 2H), 2.50 (m, 2H), 2.19 (m, 2H), 1.83 (m, 3H), 1.40 (m, 2H).

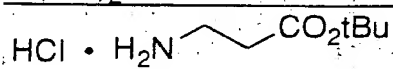
- 99 -

SCHEME 12

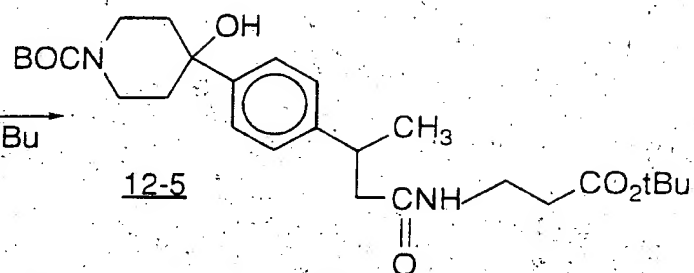


10

EDC, HOBT,
N(i-Pr)₂Et, DMF

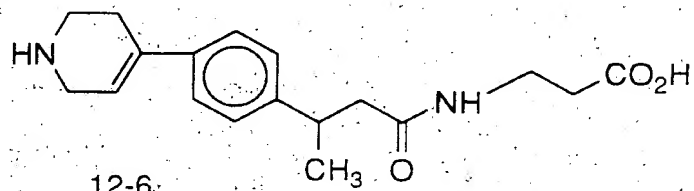


12-4

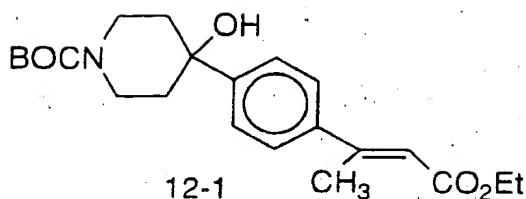


15

TFA/CH₂Cl₂



- 101 -

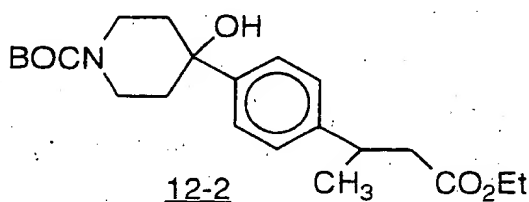


Ethyl 3-[4-(N-BOC-4-hydroxypiperidin-4-yl)phenyl]crotonate (12-1)

10 A mixture of 10-3 (500 mg, 1.4 mmol), ethyl crotonate (1.7 mL, 3.8 mmol), Pd(OAc)₂ (31 mg, 0.14 mmol), NEt₃ (0.78 mL, 8 mmol), tri-*o*-tolylphosphine (170 mg, 0.56 mmol), and CH₃CN (7 mL) was heated in a sealed tube at 100°C for 24 hours. The cooled reaction mixture was diluted with EtOAc and then washed with H₂O, 10% KHSO₄, saturated NaHCO₃, and brine, dried (MgSO₄), and concentrated. Flash chromatography (silica, 25% EtOAc/hexanes) gave 12-1 as a waxy yellow solid. R_f 0.33 (silica, 25% EtOAc/hexanes). ¹H NMR (300 MHz, CDCl₃) δ 7.49 (m, 4H), 6.16 (s, 1H), 4.23 (q, J=7Hz, 2H), 4.05 (m, 2H), 3.27 (m, 2H), 2.59 (s, 3H), 2.00 (m, 2H), 1.72 (m, 3H), 1.46 (s, 9H), 1.33 (t, J=7Hz, 3H).

15

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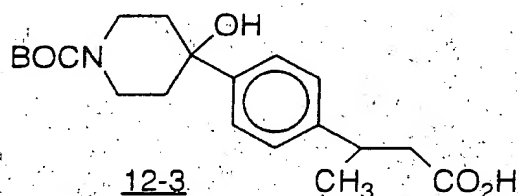
Ethyl 3-[4-(N-BOC-4-hydroxypiperidin-4-yl)phenyl]butyrate (12-2)

30 A mixture of 12-1 (400 mg, 1.0 mmol), 10% Pd/C (160 mg), and CH₃OH (5 mL) was stirred at ambient temperature under a hydrogen atmosphere for 3.0 hours. The reaction mixture was filtered through a celite pad and the filtrate concentrated to give 12-2 as a yellow oil. R_f 0.33 (silica, 30% EtOAc/hexanes).

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¹H NMR (300 MHz, CDCl₃) δ 7.45-7.20 (m, 4H), 4.10 (q, J=7Hz, 2H), 4.05 (m, 2H), 3.30 (m, 3H), 2.60 (m, 2H), 2.00 (m, 2H), 1.74 (m, 2H), 1.60 (m, 2H), 1.46 (s, 9H), 1.32 (d, J=7Hz, 3H), 1.20 (t, J=7Hz, 3H).

5



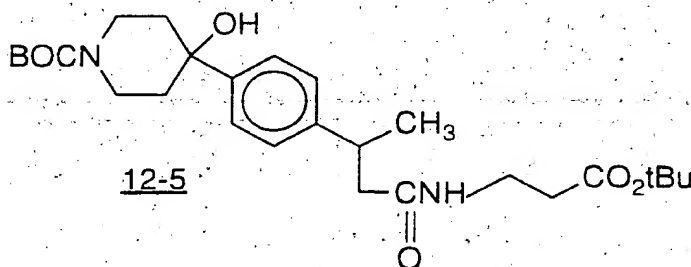
10

3-[4-(N-BOC-Hydroxypiperidin-4-yl)phenyl]butyric acid (12-3)

A mixture of 12-2 (400 mg, 1.0 mmoles), 1N NaOH (4 mL, 4.0 mmoles), and CH₃OH (5 mL) was stirred at ambient temperature for 4.0 hours. The reaction mixture was acidified with 10% KHSO₄ and then extracted with EtOAc (2x). The combined extracts were washed with brine, dried (MgSO₄), and then concentrated to give 12-3 as a white solid. R_f 0.66 (silica, 10/0.5/0.5 CH₂Cl₂/CH₃OH/HOAc).

¹H NMR (300 MHz, CDCl₃) δ 7.42 (m, 2H), 7.23 (m, 2H), 4.04 (m, 2H), 3.28 (m, 2H), 2.63 (m, 2H), 2.00 (m, 2H), 1.72 (m, 2H), 1.48 (s, 9H), 1.35 (d, J=7Hz, 3H).

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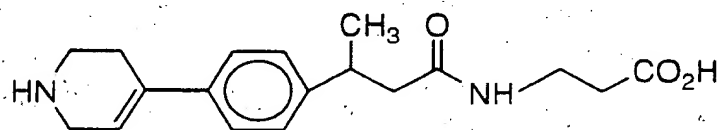
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3-[4-(N-BOC-Hydroxypiperidin-4-yl)phenyl]butyryl- β -alanine-tert-butyl ester (12-5)

To a stirred solution of 12-3 (125 mg, 0.34 mmol), 12-4 (69 mg, 0.41 mmol), HOBT (54 mg, 0.41 mmol), N(i-Pr)₂Et (228 mL, 0.82 mmol), and DMF (2 mL) at -15°C was added EDC (79 mg, 0.41 mmol) followed by removal of the cooling bath. After 20 hours the reaction mixture was diluted with EtOAc and then washed with H₂O, saturated NaHCO₃, 10% KHSO₄, and brine, dried (MgSO₄), and concentrated. Flash chromatography (silica, 60% EtOAc/hexanes) gave 12-5 as a white solid. R_f 0.26 (silica, 60% EtOAc/hexanes).

¹H NMR (300 MHz, CDCl₃) δ 7.43 (d, J=8Hz, 2H), 7.23 (d, J=8Hz, 2H), 5.88 (m, 1H), 4.03 (m, 2H), 3.32 (m, 5H), 2.41 (d, J=7Hz, 2H), 2.32 (m, 1H), 2.20 (m, 1H), 2.00 (m, 2H), 1.77 (m, 2H), 1.49 (s, 9H), 1.47 (s, 9H), 1.32 (d, J=5Hz, 3H).



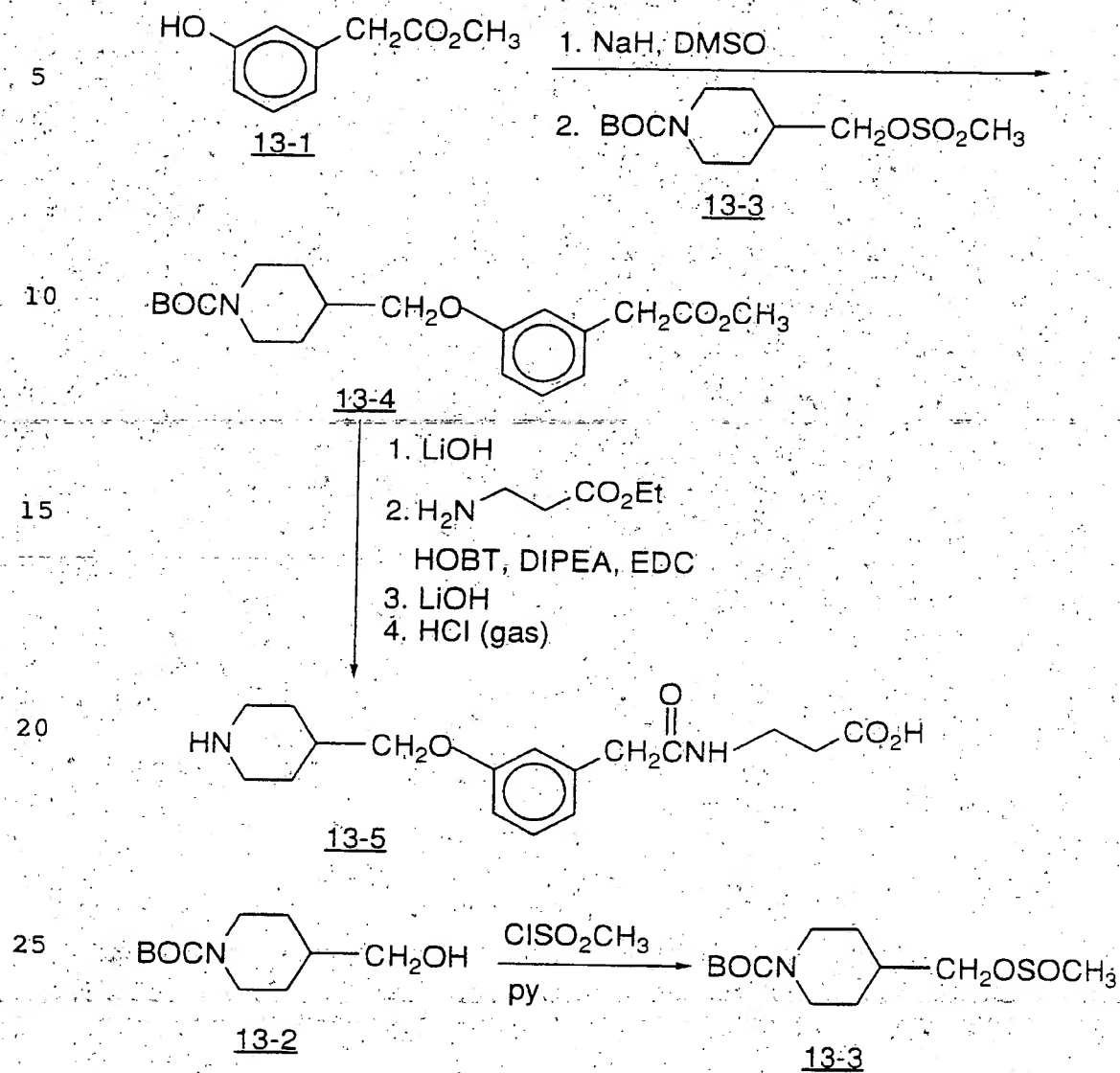
12-6

3-[4-(1,2,5,6-Tetrahydropyridin-4-yl)phenyl]butyryl- β -alanine (12-6)

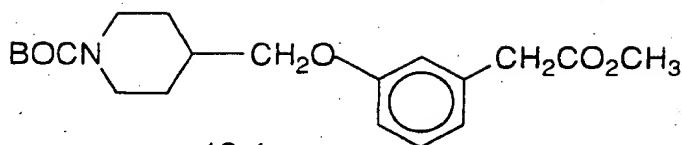
A mixture of 12-5 (120 mg, 0.25 mmol), CH₂Cl₂ (1.0 mL), and TFA (1.0 mL) was stirred at ambient temperature for 4.0 hours and then concentrated with azeotropic removal of the excess TFA. Flash chromatography (silica, 10/1/1 ethanol/NH₄OH/H₂O) gave 12-6 as a white solid. R_f 0.13 (10/1/1 ethanol/NH₄OH/H₂O).

¹H NMR (400 MHz, D₂O) δ 7.44 (d, J=8Hz, 2H), 7.27 (d, J=8Hz, 2H), 6.13 (s, 1H), 3.84 (d, J=2Hz, 2H), 3.47 (t, J=6Hz, 2H), 3.25 (m, 1H), 3.17 (m, 2H), 2.77 (m, 2H), 2.55 (m, 1H), 2.42 (m, 1H), 2.28 (m, 1H), 2.11 (m, 1H), 1.27 (d, J=7Hz, 3H).

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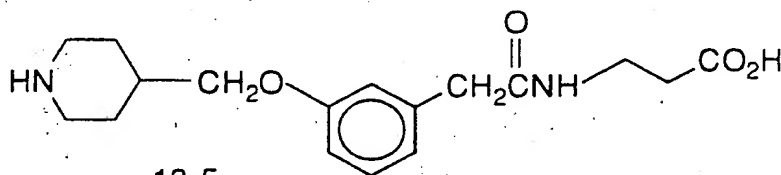
SCHEME 13

- 105 -

13-4Methyl 3-[(N-BOC-4-Piperidinyl)methoxy]phenyl acetate (13-4)

1.57 g (9.48 mmoles) of methyl 3-hydroxy-phenyl acetate (13-1) was dissolved in DMSO (5 ml) and treated with 0.36 g (9.09 mmoles) of 60% NaH (0.36 g, 9.09 mmoles) in oil. N-BOC-4-hydroxymethylpiperidine mesylate (13-3) [prepared from N-Boc-4-hydroxymethylpiperidine (13-2) by treatment with methanesulfonyl chloride and pyridine in methylene chloride] (2.79 g, 9.5 mmoles) was added in one portion and the resulting mixture heated to 60° for 8 hours and stirred at 25° for 48 hours. The reaction mixture was diluted with H₂O and Et₂O and the organic phase was washed with 1N NaOH solution, brine, then dried (Na₂SO₄) and concentrated to give 13-4 as an oil.

¹H NMR (300 MHz, CDCl₃): 1.26 (m, 2H), 1.50 (s, 9H), 1.86 (bd, 2H), 1.97 (m, 1H), 2.75 (dt, 2H), 3.60 (s, 3H), 3.70 (s, 3H), 3.80 (d, 2H), 4.08 (bd, 2H), 6.84 (m, 3H), 7.25 (dd, 1H) ppm.

13-53-[(4-Piperidinyl)methoxy]-N-(2-carboxyethyl)phenyl acetamide (13-5)

1.0 g (2.75 mmoles) 13-4 was treated with LiOH (8.25 ml of 1N) in 50 ml H₂O and 50 ml THF at 25° for 3 hours. The reaction mixture was then acidified to pH 5.5 with citric acid, concentrated and

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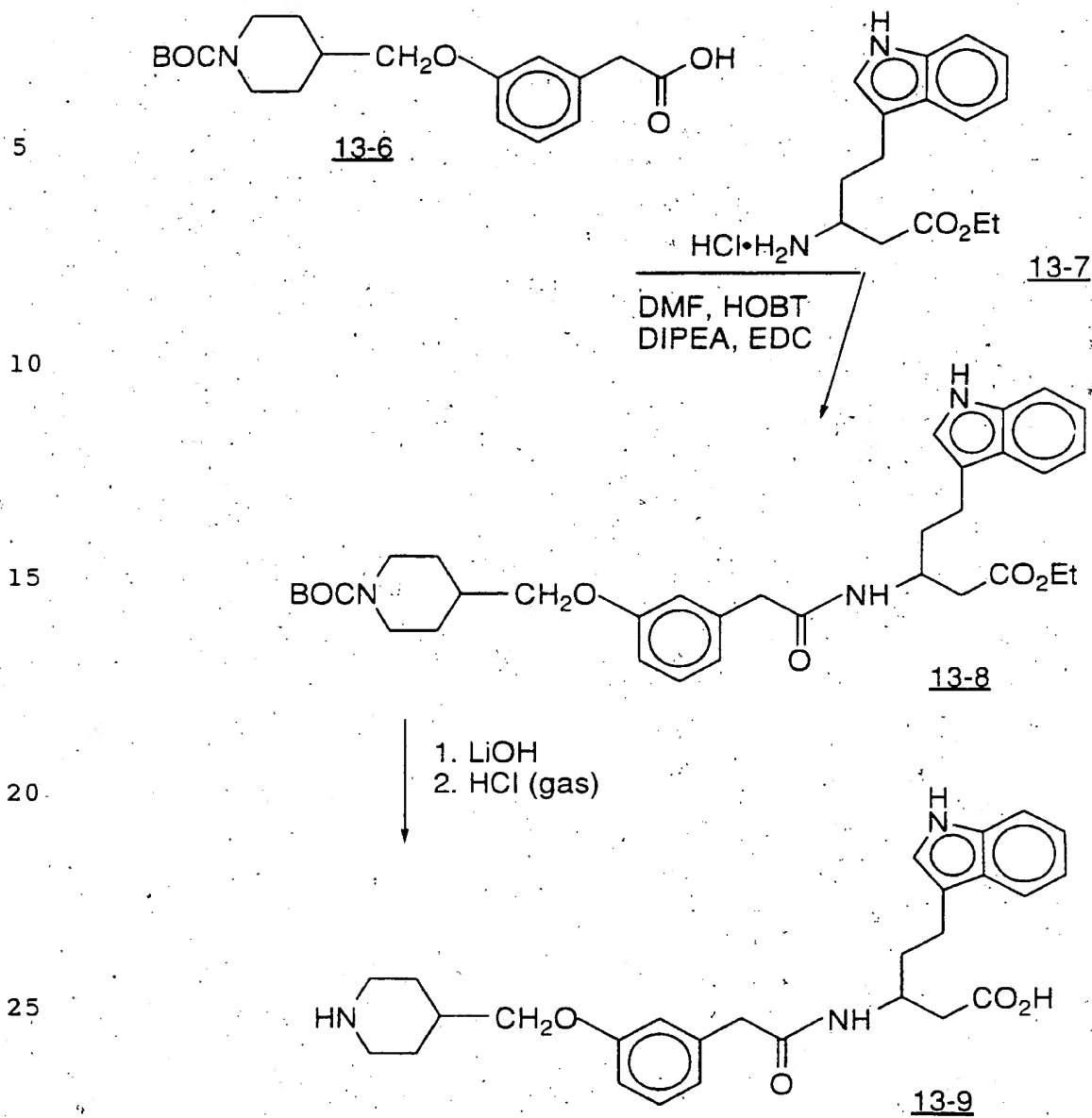
extracted with ethyl acetate. The organic extract was dried (Na_2SO_4) and concentrated to give the desired acid (13-6).

^1H NMR (partial) (300 MHz, CDCl_3): 1.25 (m, 2H), 1.24 (s, 9H), 2.75 (dt, 2H), 3.60 (s, 2H), 3.80 (d, 2H) ppm.

This acid (0.35 g, 1.0 mmoles) was dissolved in DMF (3 ml) and treated sequentially with 0.36 g (2.0 mmoles) β -alanine ethyl ester $\cdot\text{HCl}$, 0.23 g (0.15 mmoles) HOBT (1.5 mmoles), DIEA (0.53 ml, 3.0 mmoles), and 0.288g (1.5 mmoles) EDC. This mixture was stirred for 4 hours, diluted with H_2O and EtOAc and the organic phase was washed with 10% citric acid, saturated NaHCO_3 , H_2O , brine, dried (Na_2SO_4) and concentrated. The resulting oil was treated with LiOH (2.5 ml of 1N aqueous solution) as described for 13-4 to provide the desired acid. This was dissolved in EtOAc (60 ml), cooled to -15° and treated with HCl gas for 10 minutes. The solvent was removed to give 13-5 as a white powder.

^1H NMR (300 MHz, d_6 -DMSO): 1.48 (m, 2H), 1.80 (m, 2H), 2.08 (m, 1H), 2.38 (t, 2H), 2.89 (dt, 2H), 3.25 (m, 4H), 3.35 (s, 2H), 3.82 (d, 2H), 6.80 (m, 3H), 7.20 (t, 1H) ppm.

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3-[(N-BOC-4-Piperidinyl)methyloxy]-N-[ethyl 3-(2-indol-3-yl)ethyl]-
propionate]phenyl acetamide (13-8)

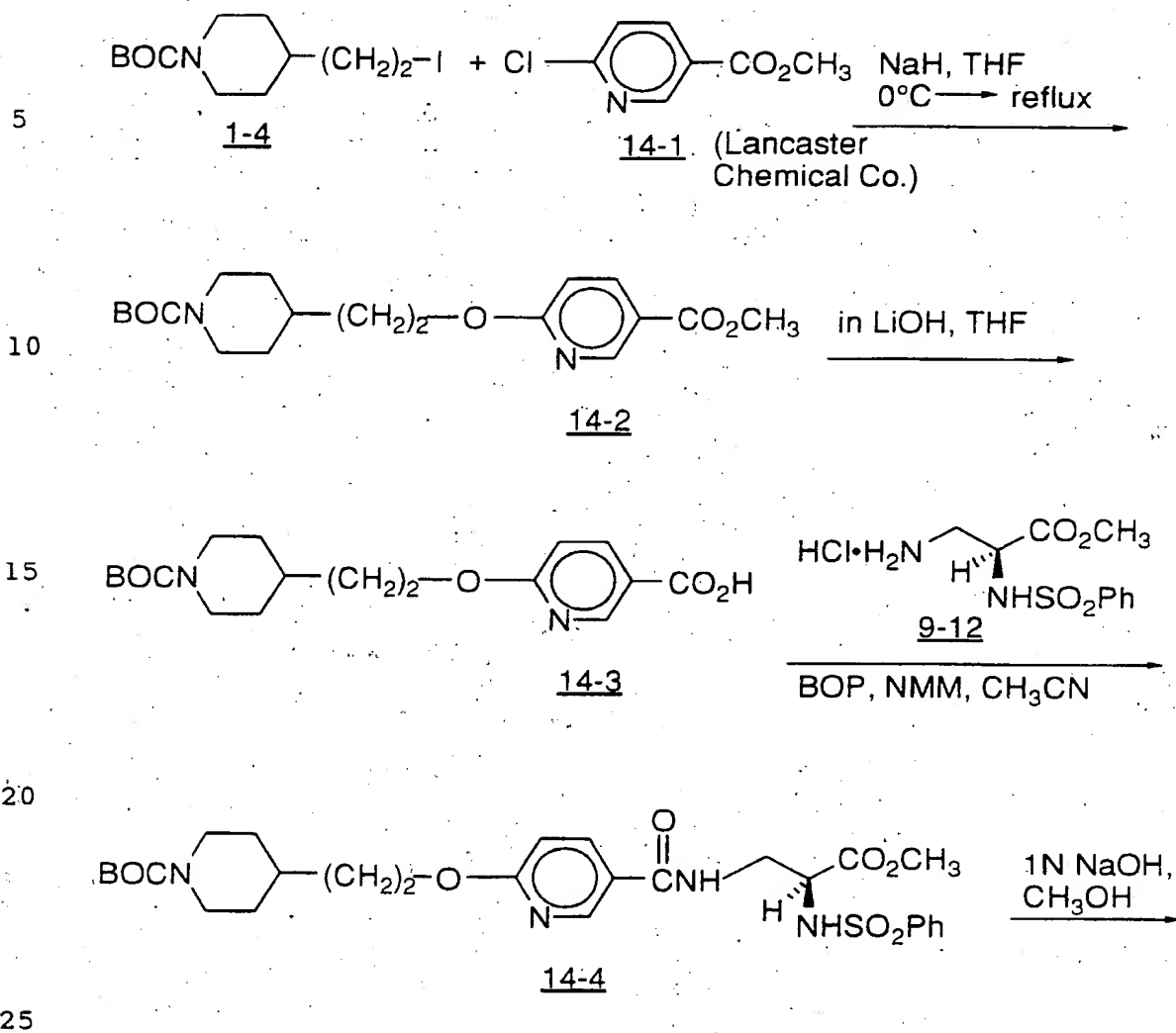
Treatment of 13-6 (0.35 g, 1.0 mmoles) in DMF (3 ml) as
described for 13-5 employing ethyl 3-[2-(indol-3-yl)ethyl]propionate
(13-7) (prepared as in Example 36, page 40, of European Publication
478,362, published April 1, 1992) provided the desired adduct 13-8.

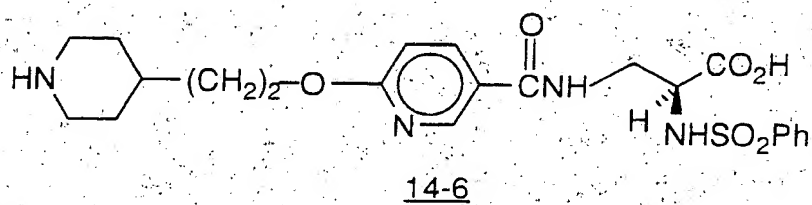
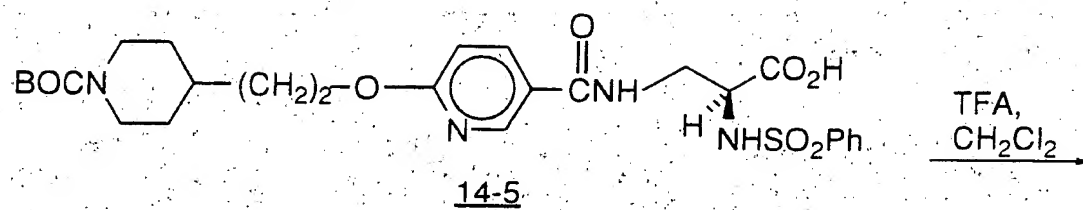
3-[(4-Piperidinyl)methyloxy]-N-[3-(2-indol-3-yl)ethyl propionic acid]-
phenyl acetamide (13-9)

Treatment of 13-8 with LiOH•H₂O and subsequently with
HCl (gas) as described for 13-5 provided 13-9 as a white solid.

¹H NMR (partial) (300 MHz, d₆-DMSO) 1.40 (m, 2H), 1.65 (d, 2H),
1.82 (m, 2H), 2.30 (m, 2H), 3.40 (s, 2H), 6.80 (m, 2H), 6.92 (m, 2H),
7.05 (m, 2H), 7.18 (t, 1H), 7.30 (d, 1H), 7.40 (d, 1H), 8.14 (d, 1H)
ppm.

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SCHEME 14



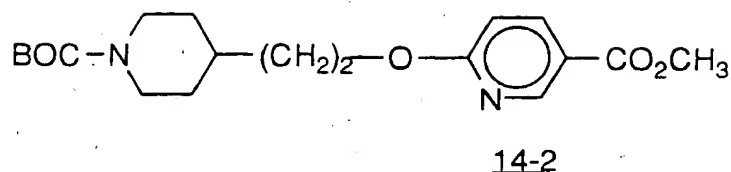
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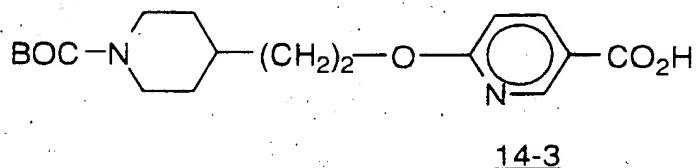
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Methyl 6-[2-(N-BOC-4-piperidiny)ethoxy]nicotinate (14-2)

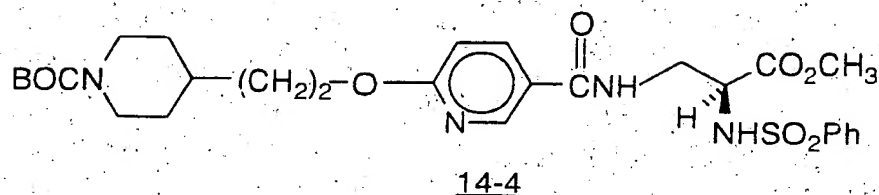
To a stirred solution of 1-4 (2.0 g, 8.8 mmol) in THF (40mL) at 0°C was added NaH (350 mg, 60% dispersion in mineral oil). After 20 min, 14-1 (750 mg, 4.4 mmol, available from Lancaster Chemical Co.) was added, followed by heating to reflux for 2 h. The cooled reaction mixture was concentrated then purified by flash chromatography (silica, 20% EtOAc/hexanes) to give 14-2 (650 mg) as a white solid R_f 0.25 (silica, 20% EtOAc/hexanes).
 1H NMR (300 MHz, CDCl₃) δ 8.83 (m, 1H), 8.17 (m, 1H), 6.77 (m, 1H), 4.37 (t, J=7Hz, 2H), 4.10 (m, 2H), 3.91 (s, 3H), 2.70 (m, 2H), 1.80-1.10 (m, 7H), 1.47 (s, 7H).



6-[2-(N-BOC-4-piperidiny)ethoxy]nicotinic acid (14-3)

A solution of 14-2 (650 mg, 1.2 mmol), 1N LiOH (3 mL), and THF (5 mL) was stirred at ambient temperature for 20h. The reaction mixture was then washed with EtOAc followed by acidification with 5% KHSO₄, then extraction with EtOAc. The EtOAc extract was washed with brine, dried (MgSO₄) and concentrated to give 14-3 (260 mg) as a white solid. R_f 0.64 (silica, 10:2:2 (CH₂Cl₂/CH₃OH/AcOH).
 1H NMR (300 MHz, CDCl₃) δ 8.89 (d, J = 2Hz, 1H), 8.21 (dd, J = 8 and 2Hz, 1H), 6.78 (d, J = 8Hz, 1H), 4.44 (t, J = 7Hz, 2H), 4.10 (m, 2H), 2.70 (m, 2H), 1.80-1.10 (m, 7H), 1.46 (s, 9H).

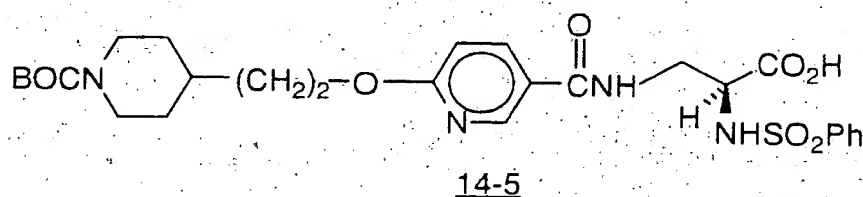
- 112 -



10 6-[2-(N-BOC-piperidin-4-yl)ethoxy]-nicotinamide-N-[Methyl 3-(2(S)-phenylsulfonylamino)propionate] (14-4)

Utilizing the procedure for converting 9-3 carboxylic acid to 9-5, 14-3 (100 mg, 0.29 mmol) gave 14-4 (130 mg) as a colorless oil after flash chromatography (silica, 60% EtOAc/hexanes). R_f 0.13 (silica, 60% EtOAc/hexanes).

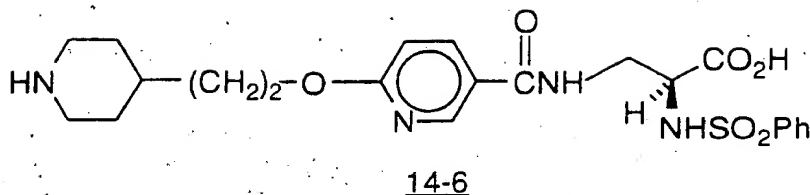
15 1H NMR (300 MHz, $CDCl_3$) δ 8.62 (d, $J = 2$ Hz, 1H), 8.03 (dd, $J = 8$ and 2 Hz, 1H), 7.55 (m, 5H), 6.80 (d, $J = 8$ Hz, 1H), 6.74 (m, 1H), 5.76 (d, $J = 8$ Hz, 1H), 4.43 (t, $J = 7$ Hz, 2H), 4.10 (m, 2H), 3.65 (s, 3H), 2.70 (m, 2H), 1.80-1.10 (m, 7H), 1.47 (s, 9H).



25 6-[2-(N-BOC-Piperidin-4-yl)ethoxy]-nicotinamide-N-[3-(2(S)-phenylsulfonylamino)propionic acid] (14-5)

30 A solution of 14-4 (120 mg, 0.21 mmol), in 1N NaOH (1 mL), and CH_3OH (1 mL) was stirred at ambient temperature for 1.0h followed by acidification with 10% $KHSO_4$. The reaction mixture was then extracted with EtOAc and the EtOAc extract washed with brine, dried ($MgSO_4$), and concentrated to give 14-5 (115 mg) as a white solid. R_f 0.48 (10:1:1 $CH_2Cl_2/CH_3OH/AcOH$).

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10 6-[2-(Piperidin-4-yl)ethoxy]nicotinamide-N-[3-(2(S)-phenylsulfonyl-amino)propionic acid] (14-6)

A solution of 14-5 (110 mg, 0.19 mmol), TFA (1.0 mL), and CH₂Cl₂ (1.0 mL) was stirred at ambient temperature for 1.0h. The solution was concentrated and then azeotroped with toluene to remove residual TFA. Flash chromatography (silica, 10:1:1 EtOH/H₂O/
15 NH₄OH) gave 14-6 (35 mg) as a white solid. R_f 0.17 (silica, 10:1:1 EtOH/H₂O/NH₄OH).

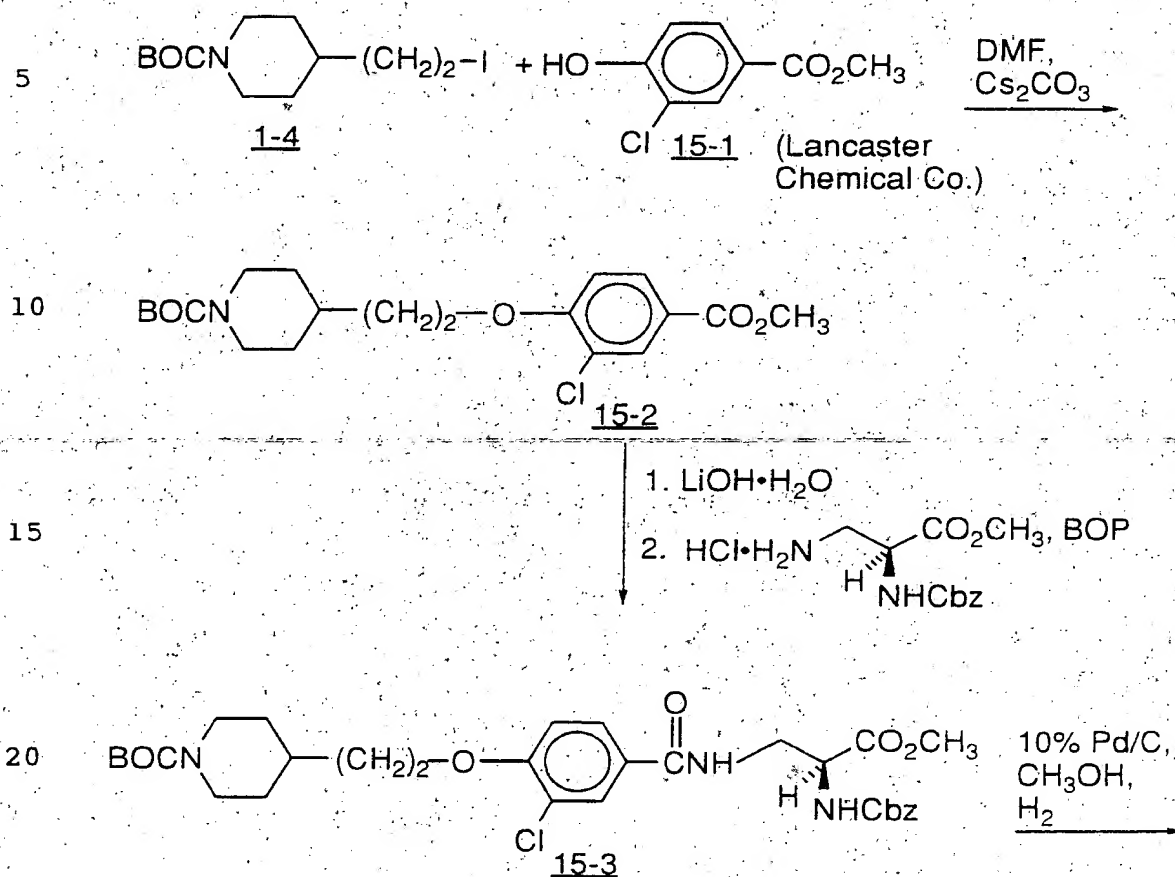
¹H NMR (300 MHz, D₂O/DCl) δ 8.46 (s, 1H), 8.44 (m, 1H), 7.78 (m, 1H), 7.42 (m, 5H), 4.57 (t, J = 7Hz, 2H), 4.25 (m, 1H), 3.79 (dd, J = 14 and 5 Hz, 1H), 3.50 (dd, J = 14 and 9 Hz, 1H), 3.40 (m, 2H), 2.97 (m,
20 2H), 2.05-1.80 (m, 5H), 1.45 (m, 2H).

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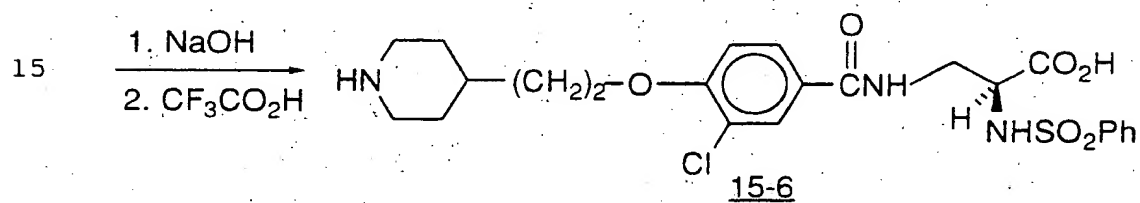
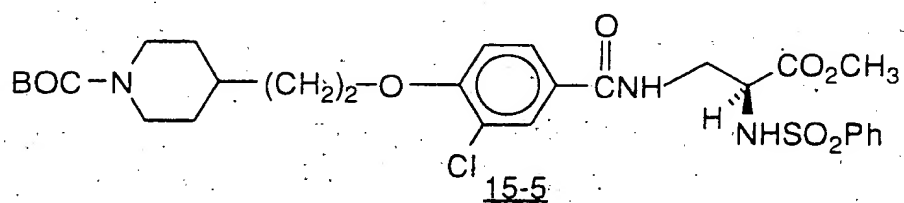
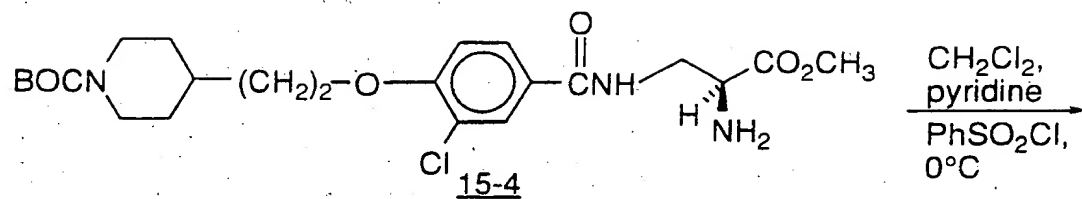
SCHEME 15



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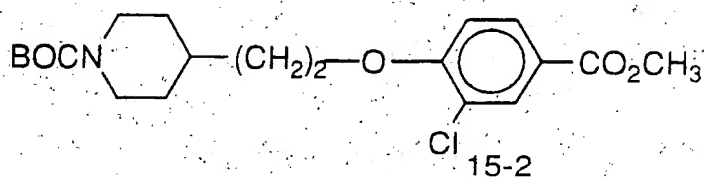


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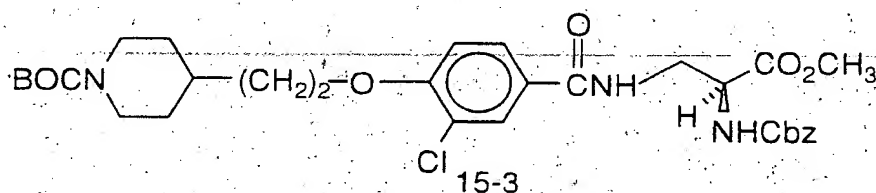
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Methyl 3-Chloro-4-[2-(N-BOC-4-piperidinyl)ethoxy]benzoate (15-2)

Utilizing the same procedure for converting 9-2 to 9-3, 15-
 1 (363 mg, 1.9 mmol) gave 15-2 (680 mg) as a colorless oil after flash
 chromatography (silica, 20% EtOAc/hexanes). R_f 0.51 (silica, 20%
 EtOAc/hexanes).

¹H NMR (300 MHz, CDCl₃) δ 8.05 (d, J=2Hz, 1H), 7.91 (dd, J=8 and
 2Hz, 1H), 6.92 (d, J=8Hz, 1H), 4.12 (t, J=7Hz, 2H), 4.09 (m, 2H), 2.71
 (m, 2H), 1.85 - 1.10 (m, 7H), 1.46 (s, 9H).

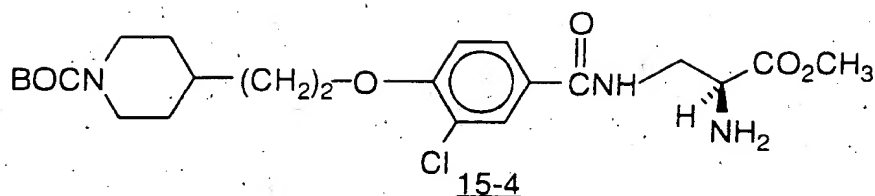


3-Chloro-4-[2-(N-BOC-piperidin-4-yl)ethoxy]phenylcarbonyl-2(S)-
 benzyloxycarbonylamino-β-alanine methyl ester (15-3)

Utilizing the same procedure for converting 9-3 to 9-5, 15-
 2 (650 mg, 1.7 mmol) gave 15-3 (630 mg) as a white solid after flash
 chromatography (silica, 50% EtOAc/hexanes). R_f 0.24 (silica, 50%
 EtOAc/hexanes).

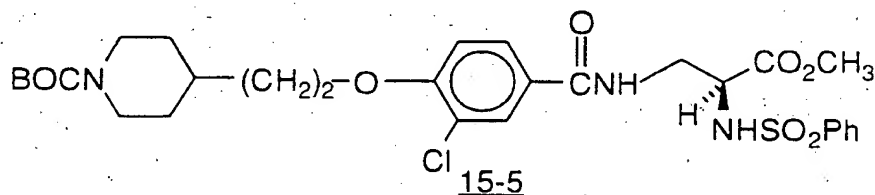
¹H NMR (300 MHz, CDCl₃) δ 7.85 (d, J= 2Hz, 1H), 7.80 (dd, J=8 and
 2Hz, 1H), 7.34 (m, 5H), 6.96 (d, J= 8Hz, 1H), 5.13 (m, 2H), 4.50 (m,
 1H), 4.14 (t, J= 7Hz, 2H), 4.08 (m, 2H), 4.78 (s, 3H), 3.46 (m, 2H),
 2.74 (m, 2H), 1.80 (m, 5H), 1.46 (s, 9H), 1.23 (m, 2H).

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3-Chloro-4-[2-(N-BOC-piperidin-4-yl)ethoxy]phenylcarbonyl-2(S)-
amino-β-alanine methyl ester (15-4)

A mixture of 15-3 (575 mg, 0.97 mmol), 10% Pd/C (230 mg), and CH₃OH (5 mL) was stirred under a hydrogen atmosphere (1 atm) at 25°C for 1.0 hour. The reaction mixture was then filtered through a celite pad and the filtrate concentrated to furnish 15-4 (422 mg) as a yellow solid. R_f 0.17 (silica, 10:0.5:0.5 CH₂Cl₂/CH₃OH/AcOH).

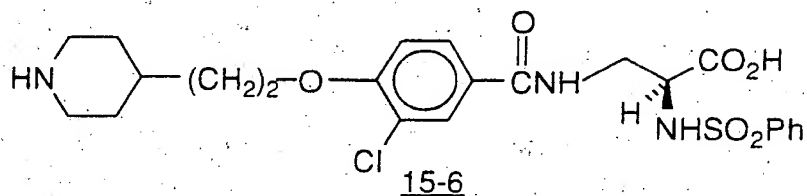


3-Chloro-4-[2-(N-BOC-piperidin-4-yl)ethoxy]phenylcarbonyl-2(S)-
phenylsulfonylamino-β-alanine methyl ester (15-5)

To a stirred solution of 15-4 (375 mg, 0.82 mmol), CH₂Cl₂ (4 mL), and pyridine (0.2 mL, 2.4 mmol) at 0°C was added phenylsulfonyl chloride (435 mg, 2.5 mmol) followed by removal of the cooling bath. After 20 hours the reaction mixture was diluted with EtOAc and then washed with H₂O, saturated NaHCO₃, 10% KHSO₄ and brine, dried (MgSO₄), and concentrated. Flash chromatography (silica, 60% EtOAc/hexanes) gave 15-5 (315 mg) as a white solid. R_f 0.26 (silica, 60% EtOAc/hexanes).

¹H NMR (300 MHz, CDCl₃) δ 7.90-7.50 (m, 7H), 6.92 (d, J=8Hz, 1H), 6.61 (m, 1H), 5.75 (m, 1H), 4.10 (t, J= 7Hz, 2H), 4.10 (m, 3H), 3.87

(m, 1H), 3.69 (m, 1H), 3.62 (s, 3H), 2.72 (m, 2H), 1.75 (m, 5H), 1.46 (s, 9H), 1.20 (m, 2H).



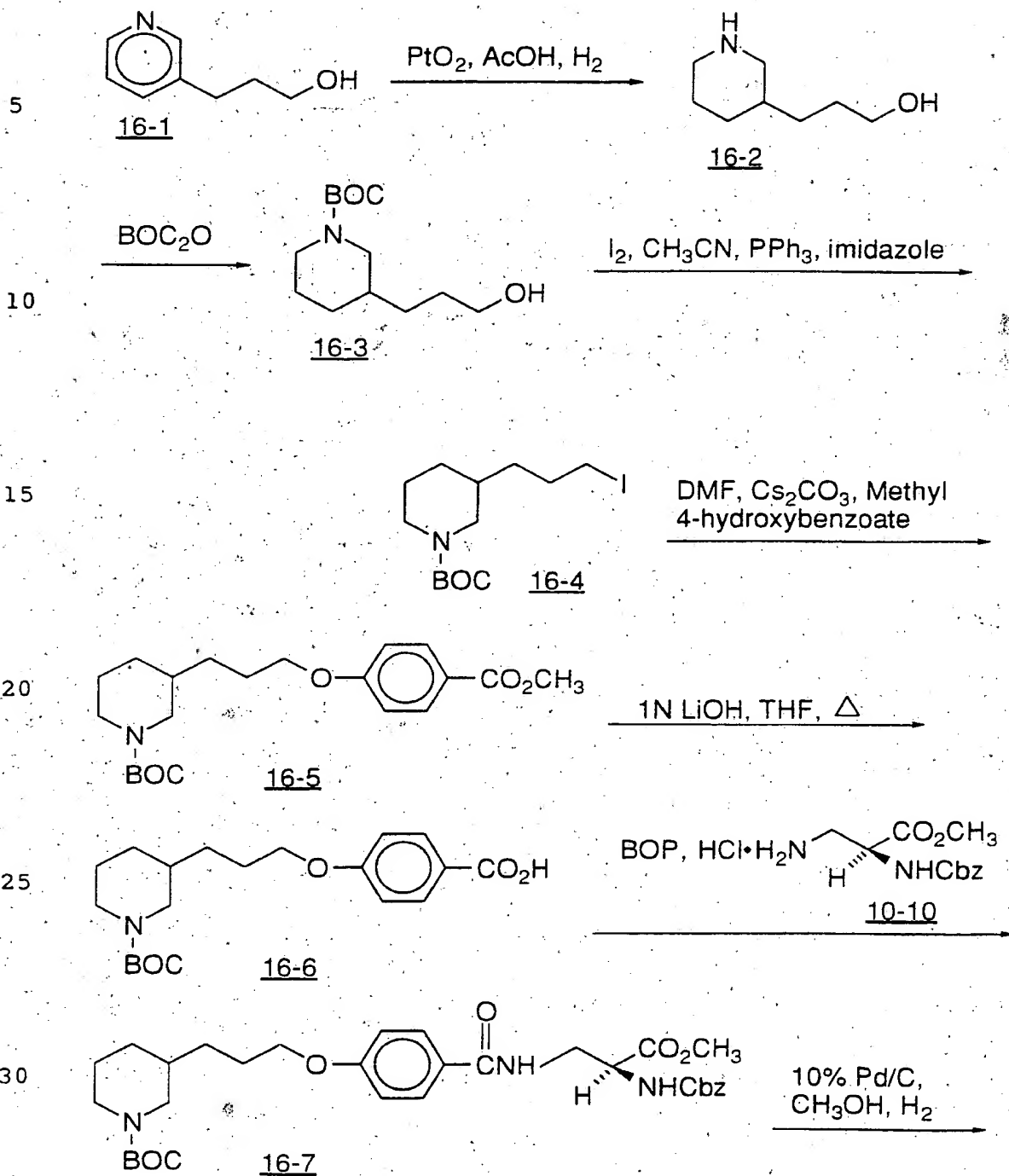
3-Chloro-4-[2-(piperidin-4-yl)ethoxy]phenylcarbonyl-2(S)-phenylsulfonamino- β -alanine (15-6)

Utilizing the procedure for converting 9-5 to 9-6, 15-5 (275 mg, 0.46 mmol) gave 15-6 (85 mg) after flash chromatography (silica, 10:1:1 ethanol/H₂O/NH₄OH). R_f 0.39 (silica, 10:1:1 ethanol/H₂O/NH₄OH).

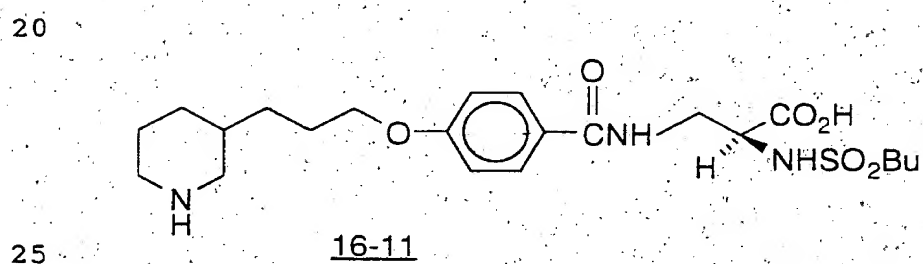
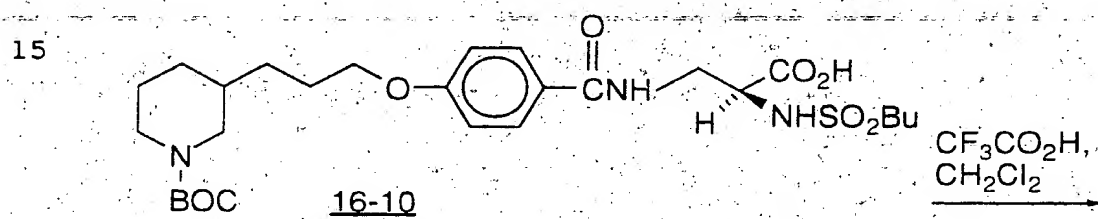
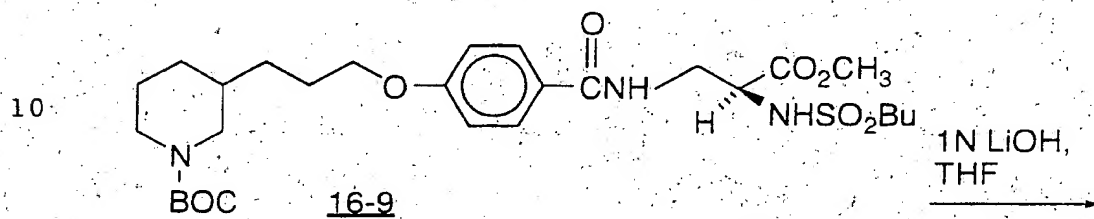
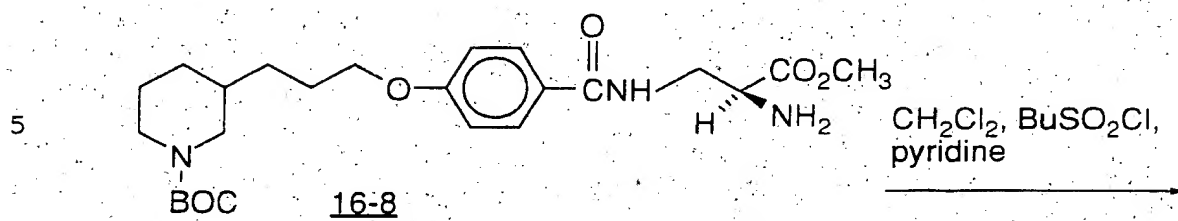
¹H NMR (300 MHz, DCl/D₂O) δ 7.70-7.00 (m, 8H), 4.23 (m, 3H), 3.75 (dd, J=14 and 4Hz, 1H), 3.40 (m, 3H), 2.97 (m, 2H), 2.10-1.80 (m, 5H), 1.46 (m, 2H).

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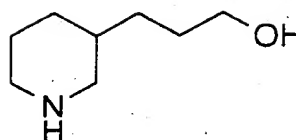
SCHEME 16



SCHEME 16 (CONTD)

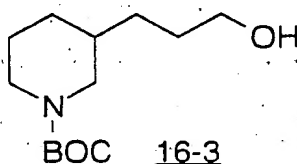


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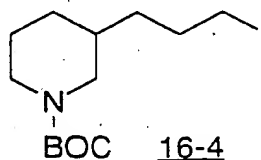
16-23-Piperidin-3-ylpropanol (16-2)

A mixture of 16-1 (Aldrich Co.) (25g, 0.18 mmol), PtO_2 (2g), and AcOH (150 mL) was shaken on the Parr apparatus at 50 PSI for 8 h. The reaction was filtered through a celite pad to give 16-2 (~25g) as a yellow oil after solvent evaporation. R_f 0.31 (silica, 4:1:1 $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}/\text{AcOH}$).

^1H NMR (400 MHz, DMSO) δ 3.32 (m, 2H), 3.19 (m, 2H), 2.62 (m, 1H), 2.37 (m, 1H), 1.80-1.00 (m, 9H).

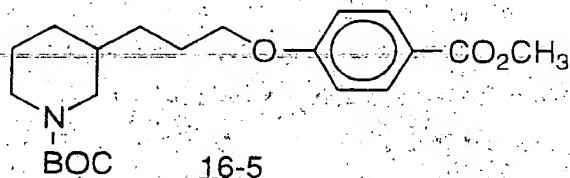
16-33-N-BOC-Piperidin-3-ylpropanol (16-3)

To a stirred solution of 16-2 (25g, ~0.18 mol), NEt_3 (30 mL, 0.22 mol), and DMF (500 mL) at 0°C was added BOC_2O (47g, 0.22 mmol). After 4 h the reaction mixture was diluted with EtOAc and then washed with 10% KHSO_4 , H_2O , sat. NaHCO_3 , and brine, dried (MgSO_4), and concentrated to give 16-3 as a yellow oil which was used directly for the next reaction. R_f 0.55 (silica, 50% EtOAc /hexanes).

16-4

3-N-BOC-Piperidin-3-ylpropyl iodide (16-4)

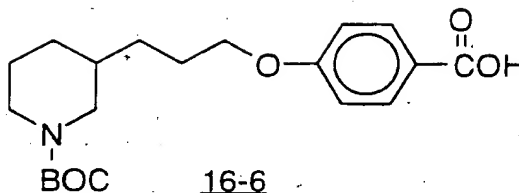
To a stirred solution of crude 16-3 (~45g, 0.18 mol), CH₃CN (500 mL), imidazole (18g, 0.27 mol), and PPh₃ (52g, 0.2 mol) at ambient temperature was added iodine (50g, 0.2 mol). After 20 h the reaction mixture was diluted with EtOAc and then washed with 10% KHSO₄, sat. Na₂SO₃, H₂O, and brine, dried (MgSO₄), and concentrated. Flash chromatography (silica, 10% EtOAc/hexanes) gave 16-4 (12g) as an oil. R_f 0.95 (silica, 50% EtOAc/hexanes). ¹H NMR (400 MHz, CDCl₃) δ 3.87 (m, 2H), 3.15 (t=7Hz, 2H), 2.77 (m, 2H), 1.90-1.00 (m, 9H), 1.45 (s, 9H).



Methyl 4-[3-(N-BOC-piperidin-3-yl)propyloxy]benzoate (16-5)

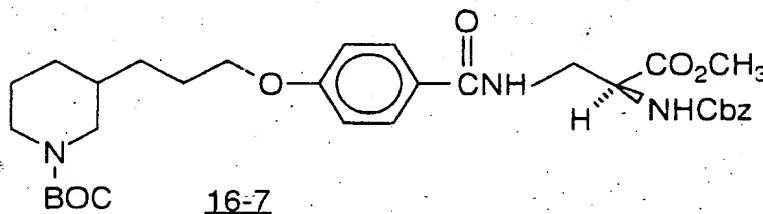
A mixture of 16-4 (1.0g, 3 mmol), methyl 4-hydroxybenzoate (Aldrich) (0.46g, 3 mmol), Cs₂CO₃ (2.9g, 9 mmol), and DMF (30 mL) was stirred at 60°C for 20 h. The cooled reaction mixture was diluted with EtOAc and then washed with H₂O (2x) and brine, dried (MgSO₄), and concentrated. Flash chromatography (silica, 15% EtOAc/hexanes) gave 16-5 (0.75g) as an oil. R_f 0.45 (silica, 30% EtOAc/hexanes). ¹H NMR (300 MHz, DCD₁₃) δ 7.97 (d, J=9Hz, 2H), 6.89 (d, J=9Hz, 2H), 4.00 (t, J=7Hz, 2H), 3.95 (m, 2H), 3.88 (s, 3H), 2.77 (m, 2H), 1.90-1.00 (m, 9H), 1.45 (s, 9H).

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4-[3-(N-BOC-Piperidin-3-yl)propyloxy]benzoic acid (16-6)

A mixture of **16-5** (0.75g, 2 mmol), THF (30 ml) and 1N
 10 LiOH (10 mL) was heated at reflux for 7 h. The cooled reaction
 mixture was diluted with EtOAc and 10% KHSO₄. The organic portion
 was then washed with brine, dried (MgSO₄) and concentrated to give
16-6 (740 mg) as a white solid. R_f 0.86 (silica, EtOAc).
 1H NMR (400 MHz, CDCl₃) δ 8.03 (d, J=8Hz, 2H), 6.95 (d, J=8Hz,
 15 2H), 4.00 (t, J=7Hz, 2H), 3.90 (m, 2H), 2.77 (m, 1H), 2.50 (m, 1H),
 1.85 (m, 4H), 1.63 (m, 2H), 1.45 (s, 9H), 1.42 (m, 2H), 1.10 (m, 1H).

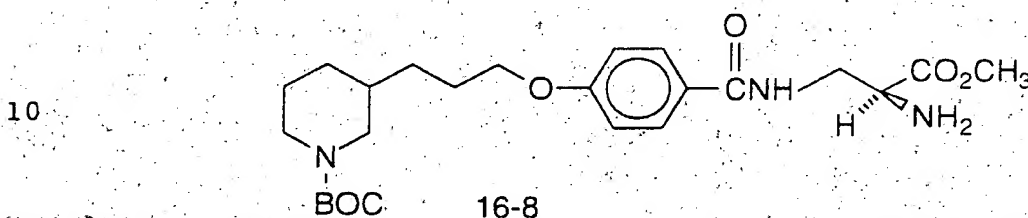


4-[3-(N-BOC-Piperidin-3-yl)propyloxy]-N-[methyl 3-(2-(S)-benzyloxycarbonylamino)propionyl]benzamide (16-7)

To a stirred solution of **16-6** (410 mg, 1.1 mmol), **10-10**
 (308 mg, 1.1 mmol), NMM (0.3 mL, 1.3 mmol), and CH₃CN (11 mL)
 at ambient temperature was added BOP reagent (0.6g, 1.3 mmol).
 20 After 20 h, the reaction mixture was diluted with EtOAc and then
 washed with 10% KHSO₄, sat. NaHCO₃, H₂O, and brine, dried
 (MgSO₄), and concentrated. Flash chromatography (silica, 60%
 EtOAc/hexanes) gave **16-7** (430 mg) as an oil. R_f 0.82 (silica, 50%
 EtOAc/hexanes).

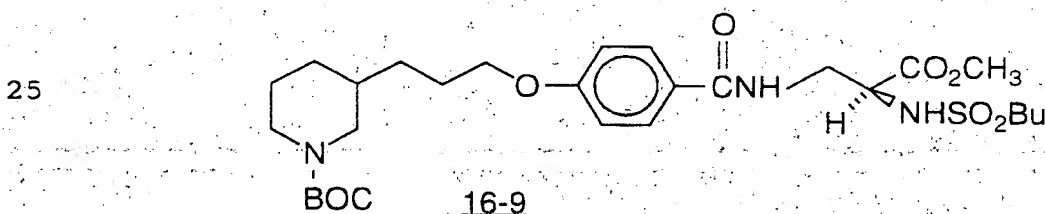
- 124 -

¹H NMR (400 MHz, CDCl₃) δ 7.70 (d, J=9Hz, 2H), 7.33 (m, 5H), 6.88 (d, J=9Hz, 2H), 7.33 (m, 5H), 6.88 (d, J=9Hz, 2H), 6.69 (m, 1H), 5.97 (m, 1H), 5.11 (s, 2H), 4.53 (m, 1H), 3.98 (t, J=7Hz, 2H), 3.93-3.80 (m, 4H), 3.76 (s, 3H), 2.77 (m, 1H), 2.50 (m, 1H), 1.80-1.00 (m, 9H), 1.45 (s, 9H).



15 4-[3-(N-BOC-Piperidin-3-yl)propyloxy]-N-[methyl 3-(2(S)-amino)-propionyl]benzamide (16-8)

A mixture of 16-7 (430 mg, 0.72 mmol), 10% Pd/C, and CH₃OH (7 mL) was stirred at ambient temperature under a hydrogen atmosphere (1 atm) for 20 h. The reaction mixture was then filtered through a celite pad and the filtrate concentrated to give 16-8 (333 mg) as an oil. R_f 0.75 (silica, 9:1:1 CH₂Cl₂/CH₃OH/AcOH).



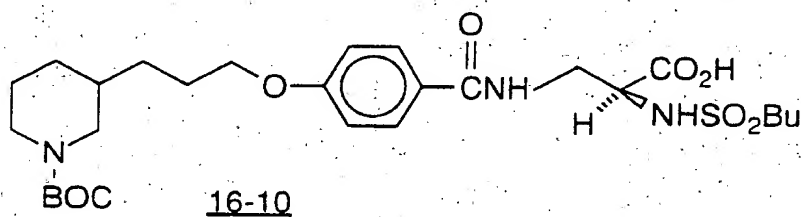
30 4-[3-(N-BOC-Piperidin-3-yl)propyloxy]-N-[methyl 3-(2(S)-butylsulfonylamino)propionyl]benzamide (16-9)

To a stirred solution of 16-8 (333 mg, 0.72 mmol), in CH₂Cl₂ (7 mL) at 0°C was added pyridine (0.12 mL, 1.4 mmol) and n-butylsulfonyl chloride (0.19 mL, 1.4 mmol), followed by removal of the cooling bath. After 20 h, the reaction mixture was diluted with

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EtOAc and then washed with 10% KHSO₄, sat. NaHCO₃. H₂O and brine, dried (MgSO₄), and concentrated. Flash chromatography (silica, 60% EtOAc/hexanes) gave 16-9 (300 mg) as a colorless oil. R_f 0.15 (silica, 50% EtOAc/hexanes).

¹H NMR (400 MHz, CDCl₃) δ 7.74 (d, J=9Hz, 2H), 6.89 (d, J=9Hz, 2H), 6.72 (m, 1H), 5.66 (m, 1H), 4.33 (m, 1H), 3.98 (t, J=7Hz, 2H), 3.90 (m, 2H), 3.82 (s, 3H), 3.77 (m, 2H), 3.03 (m, 2H), 2.78 (m, 1H), 2.50 (m, 1H), 1.90-1.00 (m, 9H), 1.45 (s, 9H), 0.91 (t, J=7Hz, 3H).

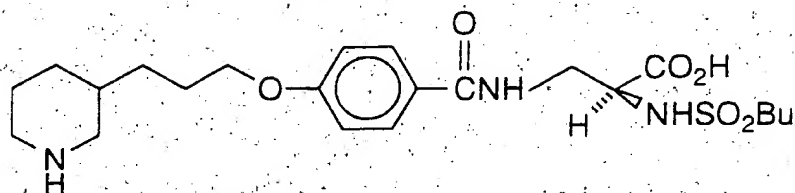


4-[3-(N-BOC-Piperidin-3-yl)propyloxy]-N-[3-(2(S)-butylsulfonyl-amino)propionic acid] benzamide (16-10)

A solution of 16-9 (300 mg, 0.5 mmol), THF (5 mL), and 1N LiOH (1.5 mL, 1.5 mmol) was stirred at ambient temperature for 30 min. The reaction mixture was acidified with 10% KHSO₄, and then extracted with EtOAc. The EtOAc extract was washed with brine, dried (MgSO₄), and concentrated to give 16-10 (273 mg) as an oil. R_f 0.87 (silica, 9:1:1 CH₂Cl₂/CH₃OH/AcOH).

¹H NMR (400 MHz, CDCl₃) δ 7.75 (d, J=9Hz, 2H), 7.14 (m, 1H), 6.89 (d, J=9Hz, 2H), 5.88 (m, 1H), 4.24 (m, 1H), 3.98 (t, J=7Hz, 2H), 4.00-3.70 (m, 4H), 3.05 (m, 2H), 2.60 (m, 2H), 1.90-1.00 (m, 9H), 1.45 (s, 9H), 0.89 (t, J=7Hz, 3H).

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16-11

4-[3-(Piperidin-3-yl)propoxy]-N-[3-(2(S)-butylsulfonylamino)-
propionic acid]benzamide (16-11)

10

A solution of 16-10 (273 mg, 0.48 mmol), TFA (2.4 mL), and CH₂Cl₂ was stirred at 25°C for 1.0 h. Concentration followed by flash chromatography (silica, 10:1:1 ethanol/NH₄OH/H₂O) gave 16-11 (70 mg) as a white solid.

15

¹H NMR (400 MHz, D₂O) δ 7.63 (d, J=9Hz, 2H), 6.90 (d, J=9Hz, 2H), 4.22 (m, 1H), 3.97 (t, J=7Hz, 2H), 3.70 (m, 1H), 3.44 (m, 1H), 3.20 (m, 2H), 2.96 (m, 2H), 2.72 (m, 1H), 2.50 (m, 1H), 1.80-1.00 (m, 9H), 0.58 (t, J=7Hz, 3H).

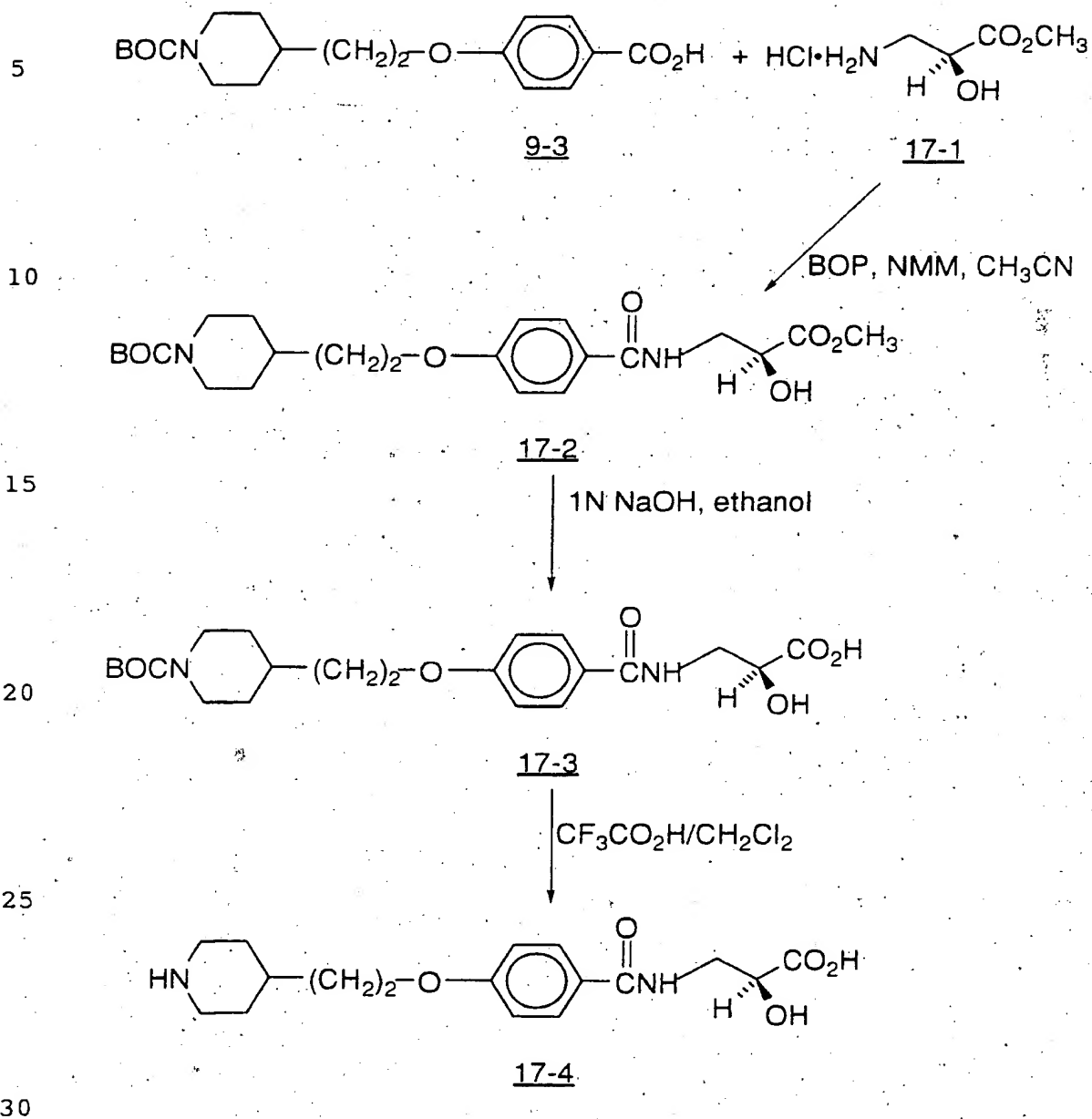
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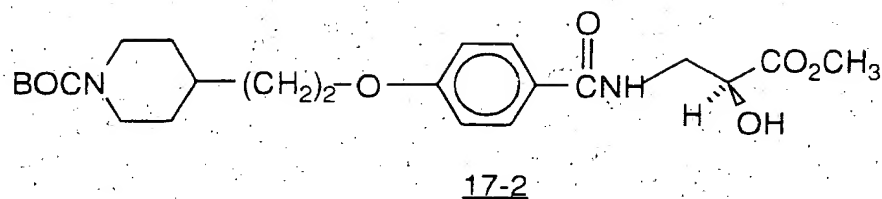
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SCHEME 17



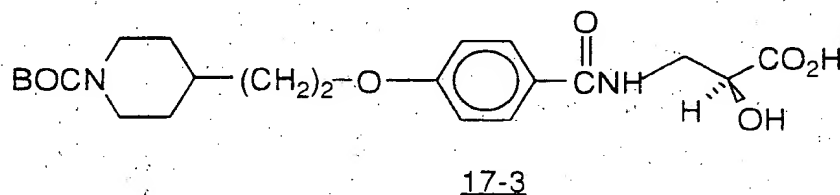
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10 4-[2-(N-BOC-Piperidin-4-yl)ethoxy]phenylcarbonyl-2(S)-hydroxy- β -alanine methyl ester (17-2)

A solution of 9-3 (60mg, 0.18 mmol), 17-1 (Pol. J. Chem 1979, 53, 1533-9) (28mg, 0.18 mmol), NMM (78 ml, 0.72 mmol), and CH₃CN (1 mL) at ambient temperature was treated with BOP (118 mg, 0.27 mmol). After 72 h, the reaction mixture was diluted with EtOAc and then washed with H₂O, sat. NaHCO₃, 10% KHSO₄, and brine, dried (MgSO₄), and concentrated. Flash chromatography (silica, 80% EtOAc/hexanes) gave 17-2 (47 mg) as a colorless oil. R_f 0.18 (silica, 80% EtOAc/hexanes).

¹H NMR (300 MHz, CDCl₃) δ 7.72 (d, J=8Hz, 2H), 6.92 (d, J=8Hz, 2H), 6.45 (m, 1H), 4.42 (m, 1H), 4.13 (m, 1H), 4.08 (m, 4H), 2.70 (m, 2H), 1.80-1.10 (m, 7H), 1.46 (s, 9H).



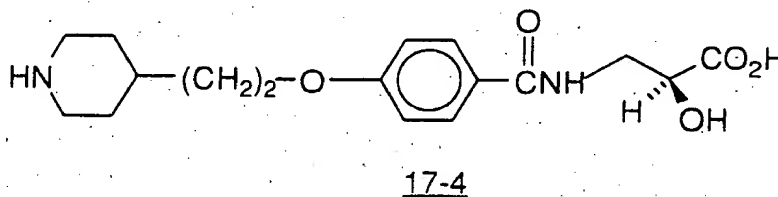
30 4-[2-(N-BOC-piperidin-4-yl)ethoxy]phenylcarbonyl-2(S)-hydroxy- β -alanine (17-3)

A solution of 17-2 (45 mg, 0.10 mmol), 1N NaOH (400 μ L), and ethanol (500 μ L) was stirred at ambient temperature for 1.0 h. The reaction was acidified with 10% KHSO₄ and then extracted with EtOAc. The EtOAc portion was washed with brine, dried (MgSO₄),

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and concentrated to give 17-3 (45 mg) as a white solid. R_f 0.26 (silica, 10:1:1 $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}/\text{AcOH}$).

^1H NMR (400 MHz, CDCl_3) δ 7.70 (m, 1H), 7.60 (d, $J=8\text{Hz}$, 2H), 6.63 (d, $J=8\text{Hz}$, 2H), 4.20-4.00 (m, 5H), 3.70-3.60 (m, 2H), 2.65 (m, 2H), 1.80-1.00 (m, 7H), 1.46 (s, 9H).



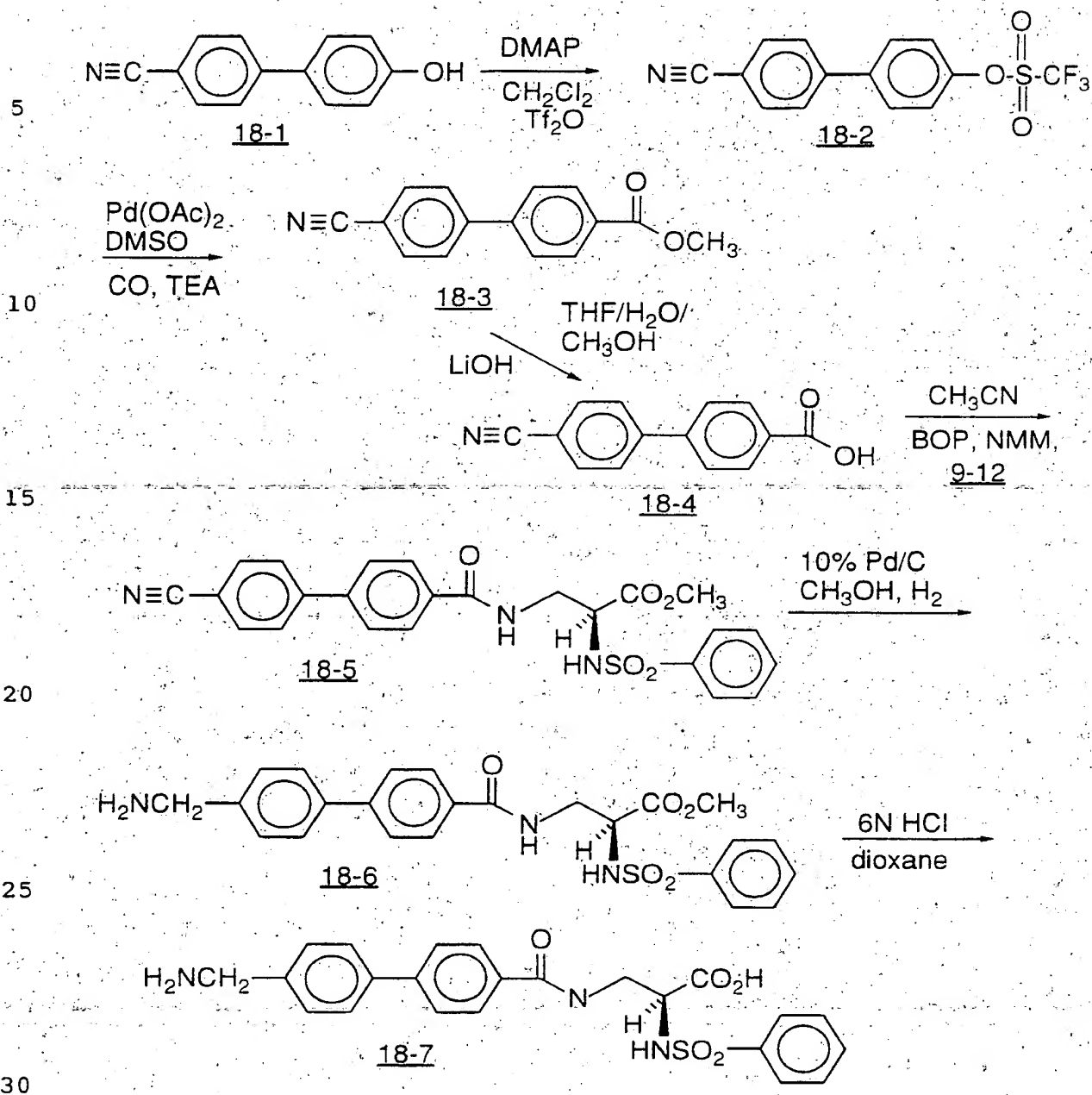
4-[2-(Piperidin-4-yl)ethoxy]phenylcarbonyl-2(S)-hydroxy- β -alanine (17-4)

A solution of 17-3 (45 mg, 0.10 mmol), TFA (1 mL), and CH_2Cl_2 (1 mL) was stirred at ambient temperature for 1.0 h.

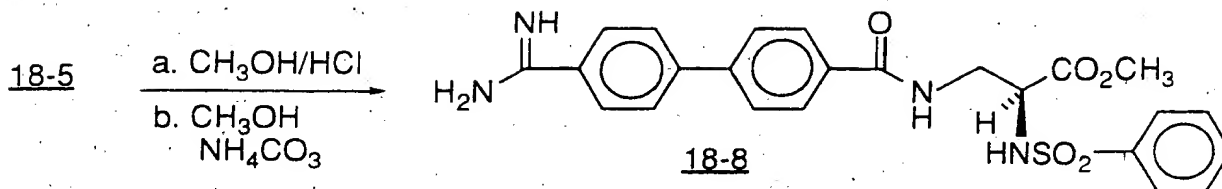
Concentration and flash chromatography (silica, 10:1:1 ethanol $\text{H}_2\text{O}/\text{NH}_4\text{OH}$) gave 17-4 (28 mg) as a white solid. R_f 0.17 (10:1:1 ethanol) $\text{H}_2\text{O}/\text{NH}_4\text{OH}$.

^1H NMR (400 MHz, $\text{DCI}/\text{D}_2\text{O}$) δ 7.73 (d, $J=8\text{Hz}$, 2H), 7.03 (d, $J=8\text{Hz}$, 2H), 4.48 (t, $J=7\text{Hz}$, 1H), 4.17 (t, $J=7\text{Hz}$, 2H), 3.73 (m, 2H), 3.40 (m, 2H), 2.95 (m, 2H), 2.00 (m, 2H), 1.87 (m, 1H), 1.79 (m, 2H), 1.46 (m, 2H).

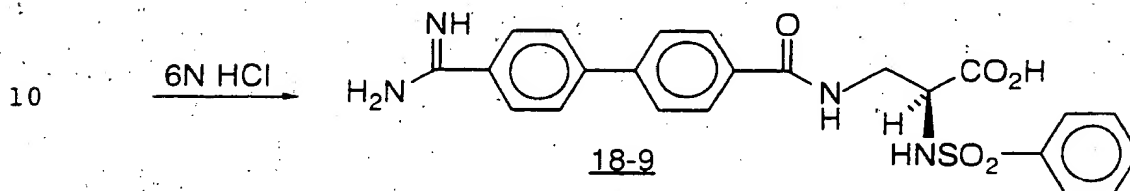
SCHEME 18



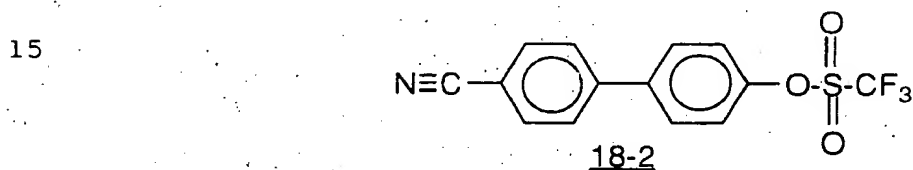
- 131 -



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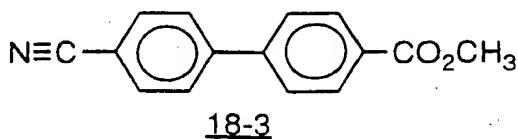


15

20 4'-Trifluorosulfonyloxy-4-biphenylnitrile (18-2)

A suspension of 4'-hydroxy-4-biphenylnitrile (18-1) (Aldrich) (5.0 g, 25.6 mmol) in 200 mL CH₂Cl₂ was cooled to -40°C and treated with 2,6 lutidine (4.5 mL, 38.4 mmol), 4-dimethylaminopyridine (0.625 g, 5.12 mmol) and trifluoromethanesulfonic anhydride (6.5 mL, 38.4 mmol). The mixture became homogeneous after
 25 warming to room temperature and was stirred for three hours, then concentrated, adsorbed onto silica and chromatographed eluting with 10% EtOAc/Hexanes to yield 18-2 as a white solid. R_f 0.3 (10% EtOAc/Hexanes).

30 ¹H NMR (400 MHz, CDCl₃) δ 7.8 (d, 2H), 7.6 (m, 4H), 7.4 (d, 2H).

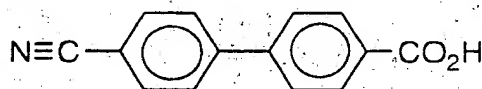


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Methyl 4'-Cyano-4-biphenylcarboxylate (18-3)

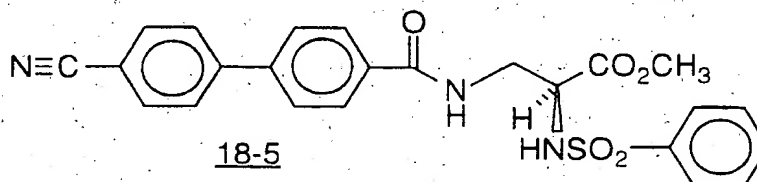
A solution of 18-2 (8 g, 24.4 mmole) in 60 mL MeOH and 35 mL DMSO was treated with triethylamine (7.8 mL, 56 mmol), Palladium Acetate (0.164 g, 0.73 mmol) and 1,3-Bis (diphenyl phosphino)propane (0.3 g, 0.73 mmol). Carbon monoxide was bubbled through the solution while the reaction was heated to reflux for five hours. The solvents were removed in vacuo and the residue purified by flash chromatography on silica gel eluting with 10% EtOAc/Hexanes to give 18-3. R_f 0.19 (10% EtOAc/Hex).

^1H NMR (300 MHz, CDCl_3) δ 8.2 (d, 2H), 7.8 (m, 4H), 7.7 (d, 2H).

18-44'-Cyano-4-biphenylcarboxylic acid (18-4)

Compound 18-3 (3.4 g, 15.1 mmole), and $\text{LiOH}\cdot\text{H}_2\text{O}$ (3.1 g, 75.5 mmol) were dissolved in THF/MeOH/ H_2O (30 mL/30 mL/-30 mL) and stirred at room temperature overnight. The solution was diluted with EtOAc and washed with 10% KHSO_4 . The organic layer was washed with brine, dried over MgSO_4 , filtered and concentrated to yield 18-4 as a white solid.

^1H NMR (400 MHz, CD_3OD) δ 8.1 (d, 1H), 7.7 (m, 4H), 7.6 (d, 2H).

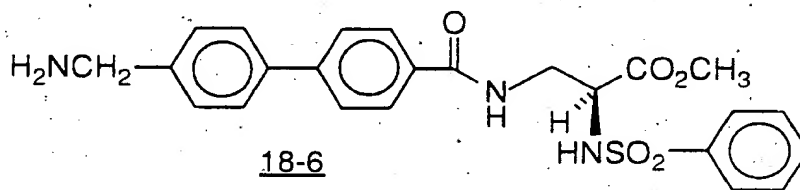
18-5

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{Methyl N-[3-(2(S)-Phenylsulphonylamino)propionate]}-4'-cyano-4-biphenylcarboxamide (18-5)

A slurry of 18-4 (1.5 g, 7.1 mmol) and 9-12 (2.0 g, 7.1 mmol) in 30 mL acetonitrile was treated with BOP (3.1 g, 7.1 mmol) at 0°C. NMM (1.5 mL, 14.2 mmol) was added and the slurry was stirred for 16 hours, then diluted with EtOAc and washed successively with H₂O, 10% KHSO₄, H₂O, sat. NaHCO₃ and brine. Concentration of the organic layer and chromatography of the residue on silica gel (eluting with 60% EtOAc/Hexanes) gave 18-5 as a white solid. R_f 0.62 (70% EtOAc/Hexanes).

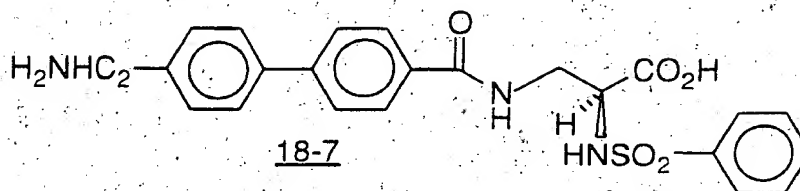
¹H NMR (400 MHz, CDCl₃) δ 7.9 (d, 2H), 7.85 (d, 2H), 7.75 (d, 2H), 7.70 (d, 2H), 7.65 (d, 2H), 7.55 (m, 1H), 7.5 (m, 2H), 4.1 (m, 1H), 3.85 (dd, 1H), 3.7 (dd, 1H), 3.6 (s, 3H).



{Methyl N-[3-(2(S)-Phenylsulphonylamino)propionate]}-4'-amino-methyl-4-biphenylcarboxamide (18-6)

A solution of 18-5 (0.5 g, 1.11 mmol) in 10 mL MeOH and 0.55 mL concentrated HCl was treated with 10% Pd/C (0.1 g) and hydrogenated under balloon pressure for 16 hours. The solution was filtered through celite and concentrated to give 18-6 as a white solid. ¹H NMR (400 MHz, CD₃OD) δ 7.85 (m, 4H), 7.75 (m, 4H), 7.6 (d, 2H), 7.5 (m, 3H), 4.25 (m, 1H), 4.2 (s, 2H), 3.8-3.5 (m, 2H), 3.5 (s, 3H).

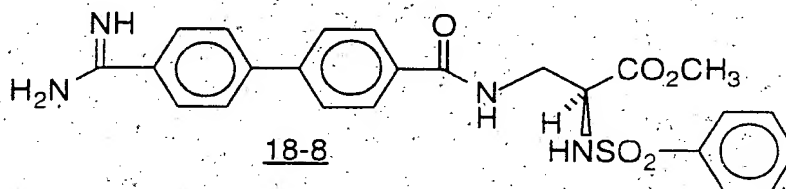
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N-[3-(2(S)-Phenylsulphonylamino)propionate]-4'-aminomethyl-4-biphenylcarboxamide (18-7)

A solution of 18-6 (0.5 g, 1.02 mmol) in 6N HCl (5 mL) and dioxane (5 mL) was stirred at room temperature for 48 hours, concentrated, and chromatographed on silica gel eluting with 10:1:1 EtOH/H₂O/NH₄OH to yield 18-7 as a white solid.

¹H NMR (400 MHz, D₂O + dTFA) δ 7.1 (m, 4H), 6.95 (d, 2H), 6.85 (d, 2H), 6.6 (s, 5H), 3.6 (m, 1H), 3.6 (s, 2H), 3.2 (dd, 1H), 2.8 (dd, 1H).

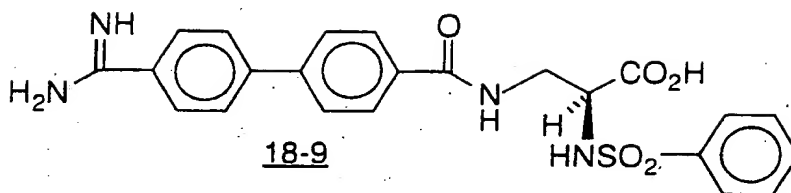


{Methyl N-[3-(2(S)-Phenylsulphonylamino)propionate]}-4'-amidino-4-biphenyl carboxamide

A solution of 18-5 (0.2 g, 0.44 mmol) in 10 mL MeOH was cooled to -20°C and saturated with HCl gas and stirred at room temperature for 16 hours. The reaction was concentrated, then dissolved in 10 mL MeOH and treated with NH₄CO₃ (0.25 g) for 16 hours. The solution was concentrated and the residue purified by flash chromatography eluting with 9:1:1 EtOH/H₂O/NH₄OH to give 18-8 as a white solid. R_f 0.25 (9:1:1 EtOH/H₂O/NH₄OH).

¹H NMR (400 MHz, CD₃OD) δ 7.9 (m, 8H), 7.8 (m, 3H), 7.5 (m, 2H), 4.2 (m, 1H), 3.7 (dd, 1H), 3.55 (m, 1H), 3.5 (s, 3H).

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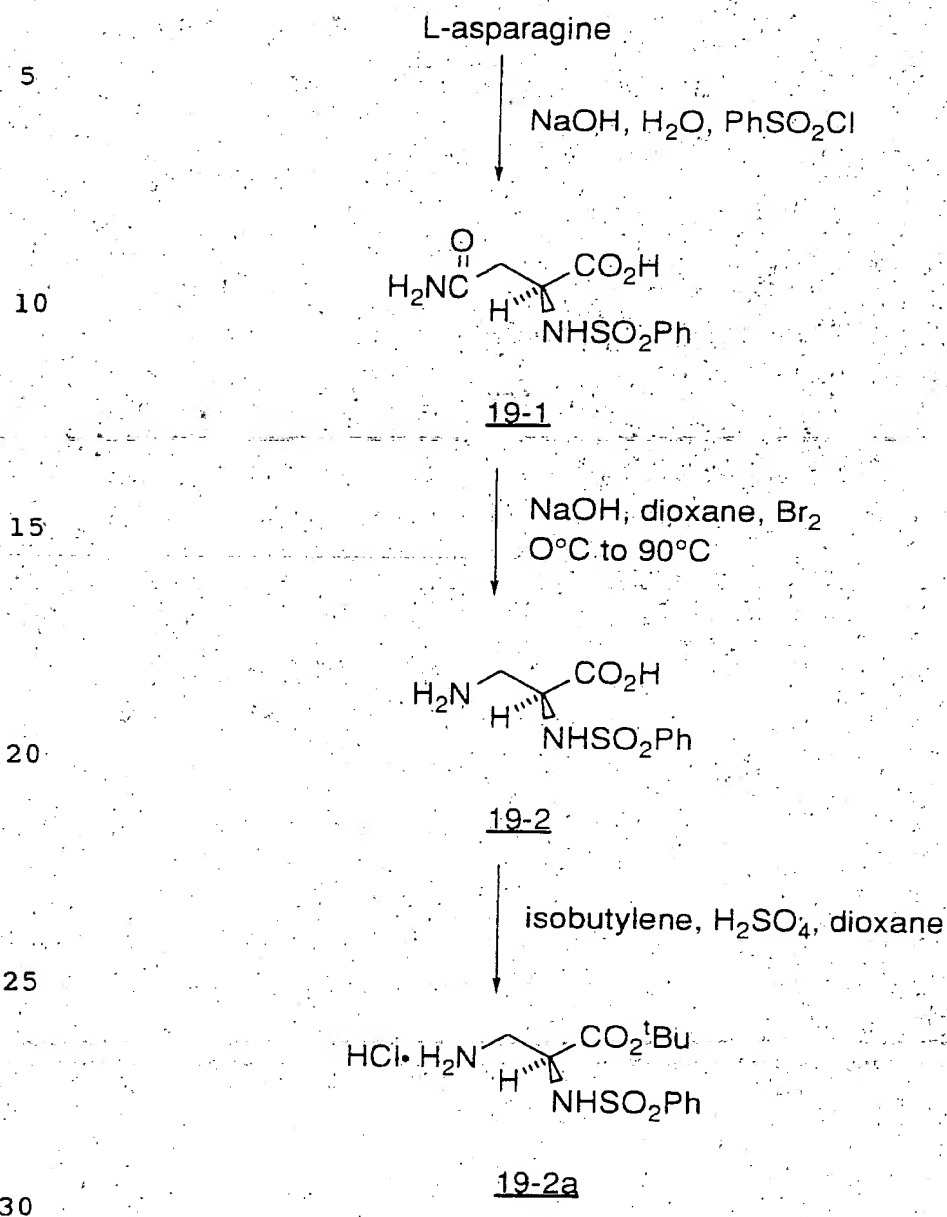


N-[3-(2(S)-Phenylsulphonylamino)propionate]-4'-amidino-4-biphenylcarboxamide (18-9)

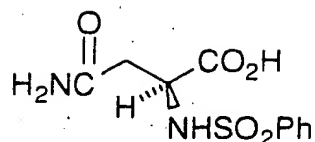
A solution of 18-8 (0.2 g, 0.42 mmol) in 5 mL 6N HCl and 2 mL dioxane was stirred 48 hours at room temperature. An additional 4 mL of 6N HCl was added and after 26 hours the solution was concentrated to yield 18-9 as a white solid.

¹H NMR (400 MHz, DMSO) δ 9.5 (s, 2H), 9.3 (s, 2H), 8.7 (m, 1H), 8.3 (d, 1H), 8.0 (m, 4H), 7.9 (s, 4H), 8.8 (d, 2H), 7.3 (m, 3H), 4.0 (m, 1H), 3.5 (m, 1H), 3.3 (m, 1H).

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SCHEME 19

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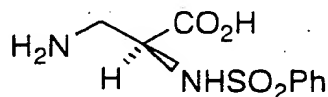


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19-1N-Phenylsulfonyl-L-asparagine (19-1)

To a stirred solution of L-asparagine (Aldrich) (10 g, 76 mmol), NaOH (3.4 g, 85 mmol), H₂O (50 mL), and dioxane (50 mL) at 0°C was added PhSO₂Cl (10.6 mL, 84 mmol). After 1 min, NaOH (3.4 g) in H₂O (50 mL) was added and the reaction mixture stirred for 30 min. The reaction mixture was then concentrated to remove the dioxane then washed with EtOAc. The aqueous phase was then cooled to 0°C and acidified to pH with conc. HCl to effect product precipitation. The resulting solid was collected by filtration, washed with H₂O (20 mL) and dried at 50°C under vacuum to give 19-1 as a white solid. R_f 0.40 (silica, 10:1:1 ethanol/H₂O/NH₄OH). ¹H NMR (300 MHz, D₂O) δ 7.59 (m, 2H), 7.26 (m, 3H), 3.92 (m, 1H), 3.02 (m, 1H), 2.35 (m, 1H).

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25

19-22(S)-Phenylsulfonylamino-3-aminopropionic acid (19-2)

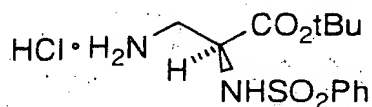
To a stirred solution of NaOH (15.6 g, 0.4 mol) in H₂O (70 mL), cooled with an icebath, was added bromine (3.6 mL, 0.07 mol) dropwise. After 5 min, a cold solution of 19-1 (14.6 g, 54 mmol) and NaOH (4.3 g, 0.1 mol) in H₂O (50 mL) was added in one portion. The solution was stirred for 20 min at 0°C then 30 min at 90°C. The reaction mixture was recooled to 0°C and the pH adjusted to 7 through

30

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dropwise addition of conc. HCl. The white precipitate formed was collected by filtration and dried to give 19-2 as a white solid.

^1H NMR (300 MHz, D_2O) δ 8.00 7.50 (m, 5H), 3.88 (m, 1H), 3.37 (m, 1H), 3.12 (m, 1H).

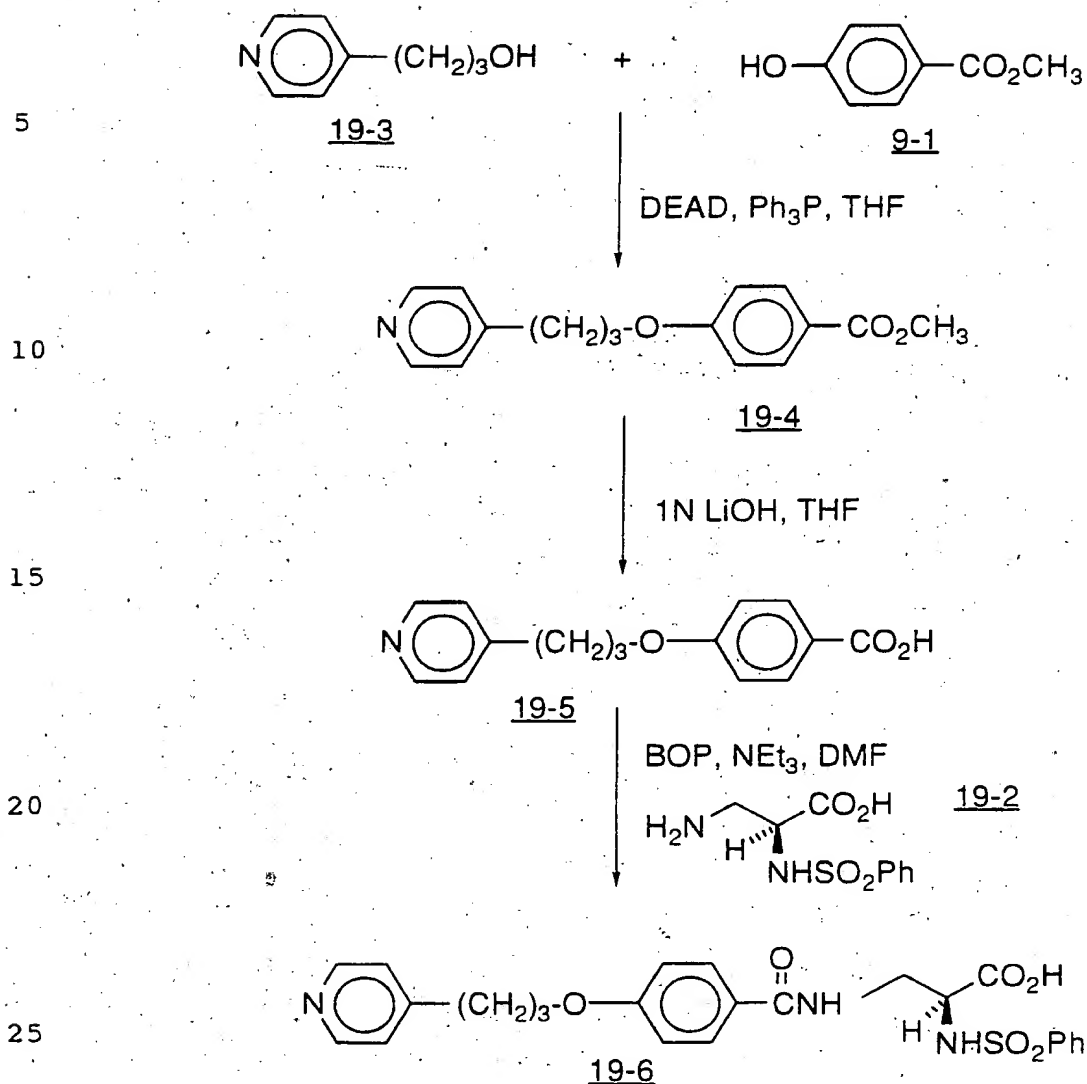
19-2a

tert-Butyl 2(S)-phenylsulfonylamino-3-aminopropionate hydrochloride (19-2a)

In a Fischer-Porter tube, a mixture of 19-2 (10.2 g, 42 mmol) and DME (150 mL) was sequentially, treated with H_2SO_4 (6.4 mL, 0.12 mol), cooled to -78°C , and then condensed with isobutylene (75 mL). The cooling bath was removed. After 2h, ice/water (250 mL) was added followed by washing with ether (2x). The aqueous phase was basified with aq 6N NaOH, saturated with NaCl, and extracted with EtOAc (3x). The combined extracts were washed with brine, dried (MgSO_4), and concentrated to give a white solid. This was dissolved in CHCl_3 then treated with 1N HCl/ether (22 mL) then concentrated to give 19-2a as a glossy yellow solid.

^1H NMR (400 MHz, DMSO) δ 8.25-8.00 (m, 4H), 7.85-7.58 (m, 5H), 4.08 (m, 1H), 3.10 (m, 1H), 2.73 (m, 1H), 1.17 (s, 9H).

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SCHEME 19 (CONT'D)Methyl 4-[3-(Pyridin-4-yl)propoxy]benzoate (19-4)

30 To a stirred solution of 9-1 (Aldrich) (2.0 g, 13.2 mmol), PPh₃ (4.3 g, 16.4 mmol), 19-3 (Aldrich) (2.0 g, 14.5 mmol), and THF (60 mL) at ambient temperature was added diethyl azodicarboxylate (DEAD) (2.9 g, 2.6 mL, 16.4 mmol) in THF (10 mL) dropwise over a 5 min period. After stirring overnight, the reaction mixture was diluted with EtOAc and then washed with H₂O, sat. NaHCO₃ and brine,

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dried (MgSO₄) and concentrated. Flash chromatography (silica, 50% EtOAc/hexanes) gave 19-4 as a colorless oil. R_f 0.22 (silica, 50% EtOAc/hexanes).

5 ¹H NMR (300 MHz, CDCl₃) δ 8.51 (m, 2H), 8.00 (m, 2H), 7.18 (m, 2H), 6.89 (m, 2H), 4.02 (t, J = 7 Hz, 2H), 3.89 (s, 3H), 2.85 (t, J = 7 Hz, 2H), 2.15 (m, 2H).

4-[3-(Pyridin-4-yl)propyloxy]benzoic acid (19-5)

10 A solution of 19-4 (3.2 g, 11.9 mmol), 1N LiOH (25 mL), and THF (50 mL) was stirred overnight at ambient temperature. After 20 h, the solution was washed with EtOAc and then acidified with 10% KHSO₄ to give a suspension of white solid. The aqueous portion was extracted with CHCl₃ and then the aqueous portion containing the solid was filtered. After drying the solid at 50°C for 3 h, 19-5 was obtained.

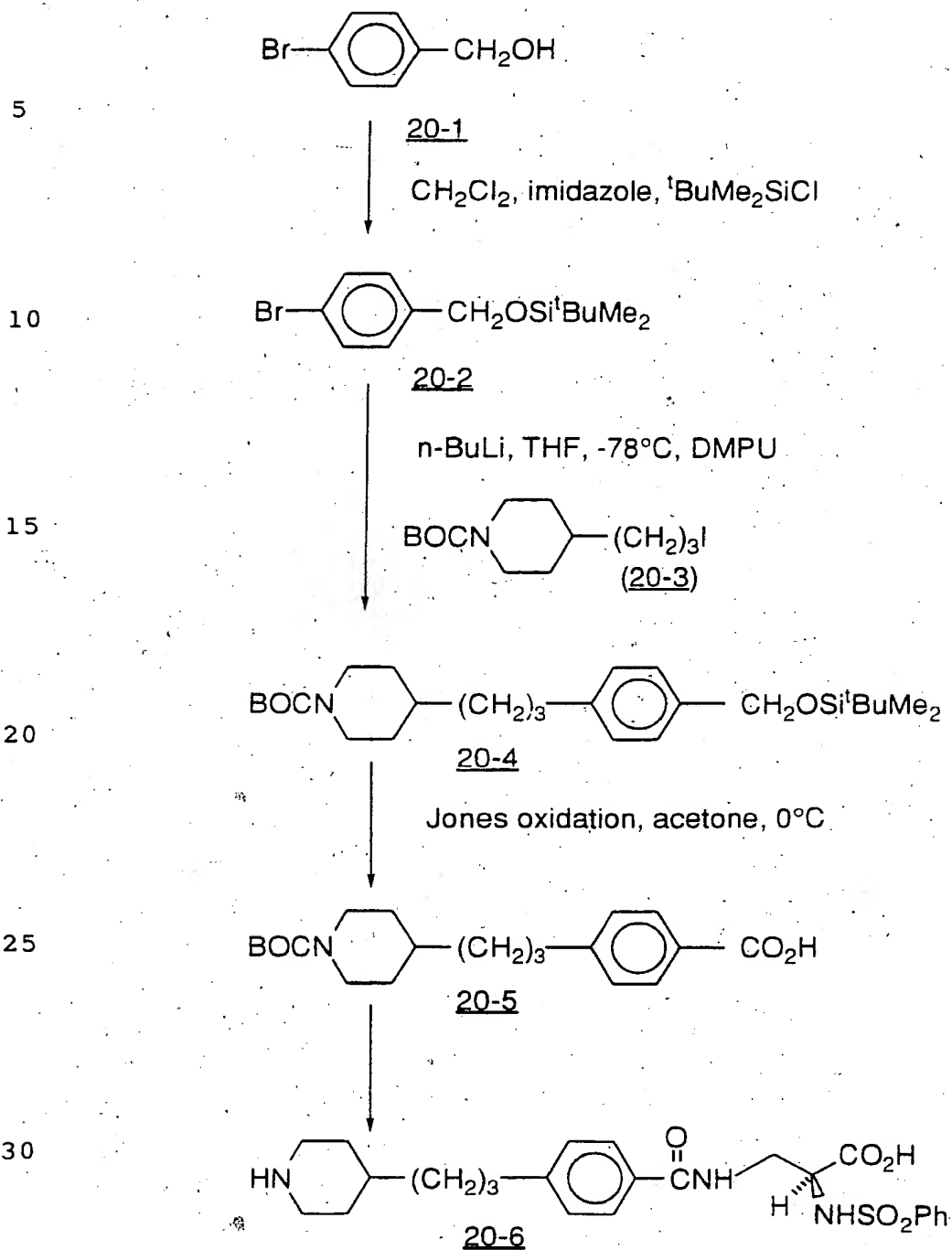
15 R_f 0.47 (silica, 10/1/1 CH₂Cl₂/CH₃OH/AcOH).
¹H NMR (300 MHz, D₂O + K₂CO₃) δ 8.00 (m, 2H), 7.69 (m, 2H), 6.68 (m, 2H) 6.53 (m, 2H), 3.50 (m, 2H), 2.23 (m, 2H), 1.55 (m, 2H).

20 4-[3-(Pyridin-4-yl)propyloxy]benzoyl-2(S)-phenylsulfonylamino-β-alanine (19-6)

A solution of 19-5 (200 mg, 0.78 mmol), NEt₃ (0.22 mL, 1.5 mmol), and DMF (4 mL) at ambient temperature was treated with BOP (345 mg, 0.78 mmol). After 3.0 h, NEt₃ (0.22 mL, 1.5 mmol) and 19-2 (190 mg, 0.78 mmol) were added. After 20 h, the reaction mixture was concentrated and subjected to flash chromatography (silica, 10/1/1 CH₂Cl₂/CH₃OH/AcOH) to give impure 19-6 (400 mg). Prep HPLC purification (Delta Pak C-18 Å column, 0 to 100% CH₃CN/H₂O containing 0.1% trifluoroacetic acid) gave pure 19-6 as a white solid after lyophilization. R_f 0.74 (silica, 10/1/1 CH₂Cl₂/CH₃OH/AcOH).

30 ¹H NMR (400 MHz, D₂O) δ 8.38 (m, 2H), 7.72 (m, 2H), 7.51 (m, 2H), 7.33 (m, 2H), 7.28 (m, 3H), 6.93 (m, 2H), 4.13 (t, J = 6 Hz, 2H), 3.84 (dd, J = 10 and 4 Hz, 1H), 3.64 (dd, J = 14 and 4 Hz, 1H), 3.32 (dd, J = 14 and 10 Hz, 1H), 2.88 (t, J = 7 Hz, 2H), 2.18 (m, 2H).

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SCHEME 20

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4-Bromobenzyl alcohol t-butyldimethylsilyl ether (20-2)

A stirred solution of 20-1 (Aldrich; 3.0 g, 16.0 mmol) in CH₂Cl₂ (80 mL) at ambient temperature was treated sequentially with imidazole (1.2 g, 17.6 mmol) and tert-butyldimethylsilyl chloride (2.7 g, 17.6 mmol). After 1.5 h the reaction mixture was washed with H₂O and brine, dried (MgSO₄) and concentrated to give 20-2 as a yellow oil. R_f 0.70 (silica, 10% EtOAc/hexanes).

¹H NMR (300 MHz, CDCl₃) δ 7.34 (d, J = 8 Hz, 2H), 7.09 (d, J = 8 Hz, 2H), 4.07 (s, 2H), 0.85 (s, 9H), 0.99 (s, 6H).

4-[3-(N-Boc-Piperidin-4-yl)propyl]benzyl alcohol t-butyldimethylsilyl ether (20-4)

A stirred solution of 20-2 (401 mg, 1.33 mmol) in THF (13 mL) at -78°C was treated with n-BuLi (0.9 mL, 1.46 mmol; 1.6 M/hexanes). After 5 min., 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU) (0.32 mL, 2.7 mmol) was added followed by addition of 20-3 (471 mg, 1.33 mmol; see European Publication 478,328 for preparation) in THF (1 mL) after 5 min. The cooling bath was removed after 15 min and the reaction was stirred overnight. After 16 hours, the reaction was diluted with EtOAc and then washed with H₂O and brine, dried (MgSO₄), and concentrated. Flash chromatography (silica, 5% EtOAc/hexanes) gave 20-4 as a yellow oil. R_f 0.81 (silica, 10% EtOA/hexanes).

¹H NMR (400 MHz, CDCl₃) δ 7.14 (d, J = 8 Hz, 2H), 7.03 (d, J = 8 Hz, 2H), 4.62 (s, 2H), 3.96 (m, 2H), 2.56 (m, 2H), 2.48 (t, J = 7 Hz, 2H), 1.60-0.90 (m, 9H), 1.36 (s, 9H), 0.85 (s, 9H), 0.00 (s, 6H).

4-[3-(N-BOC-Piperidin-4-yl)propyl]benzoic acid (20-5)

To a vigorously stirred solution of 20-4 (230 mg, 0.51 mmol) in acetone (5 mL) at 0°C was added Jones Reagent dropwise until the color changed from green to orange. The excess Jones Reagent was quenched with isopropanol (1 mL) followed by stirring for 15 min. The reaction mixture was diluted with EtOAc and then washed with

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H₂O and brine, dried (MgSO₄) and concentrated to give 20-5 as a yellowish oil.

¹H NMR (400 MHz, CDCl₃) δ 8.01 (d, J = 8 Hz, 2H), 7.25 (d, J = 8 Hz, 2H), 4.02 (m, 2H), 2.63 (m, 2H), 1.70-1.00 (m, 9H), 1.42 (s, 9H).

4-[3-(Piperidin-4-yl)propyl]benzoyl-2(S)-phenyl-sulfonylamino-β-alanine (20-6)

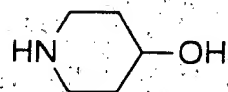
20-5 was treated with 9-12 as described for 18-5 to afford the desired ester which was hydrolyzed as described for 18-7 to provide 20-6. R_f 0.4 (silica, ethanol/H₂O/NH₄OH 10:1:1).

¹H NMR (400 MHz, D₂O) δ 7.59 (m, 2H), 7.32 (d, 2H), 7.17 (m, 5H), 4.08 (m, 1H), 3.62 (dd, 1H), 3.30 (dd, 1H), 3.20 (m, 2H), 2.77 (m, 2H), 2.52 (t, 2H), 1.80-1.10 (m, 9H).

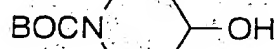
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SCHEME 21

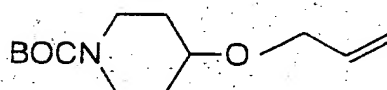
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21-1 (Aldrich)

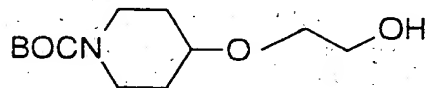
10

BOC₂O, dioxane/H₂O, Na₂CO₃21-2

15

NaH, DMF;
allyl bromide21-3

20

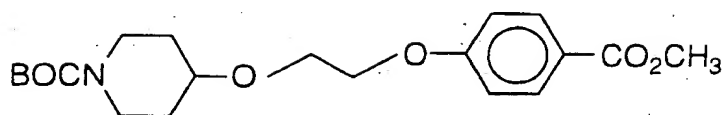
a) O₃, CH₂Cl₂/CH₃OH, -78°C
b) NaBH₄21-4

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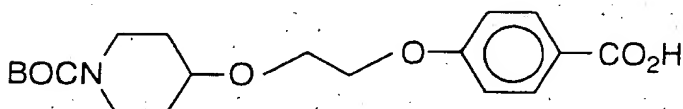
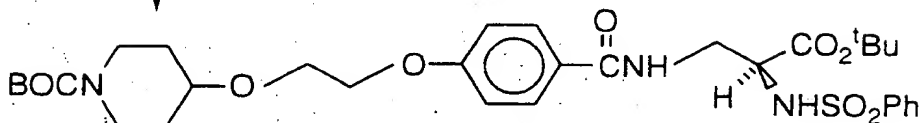
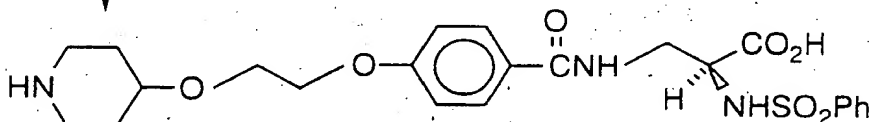
9-1, DEAD, PPh₃, THF

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21-5

1N NaOH, EtOH

21-6EDC, DMF, 19-2a21-7TFA/CH₂Cl₂/anisole21-8N-Boc-4-Hydroxypiperidine (21-2)

A stirred solution of 21-1 (9.4 g, 93 mmol), dioxane (100 mL), and 8% Na₂CO₃ (100 mL) at ambient temp. was treated with BOC₂O (23 g, 0.11 mmol). The reaction was continued for 30 min. while maintaining the pH at 8-10 with addition of Na₂CO₃. The dioxane was then evaporated and the residue diluted with H₂O and extracted with EtOAc (2x). The combined extracts were washed with

brine, dried (MgSO_4), and concentrated to give 21-2 as an off-white solid. R_f 0.25 (silica, 50% EtOAc/hexanes).

^1H NMR (400 MHz, CDCl_3) δ 3.85 (m, 3H), 3.01 (m, 2H), 1.85 (m, 2H), 1.46 (m, 2H), 1.44 (s, 9H).

3-[(N-Boc-Piperidin-4-yl)oxy]propene (21-3)

To a suspension of NaH (0.48 g, 11.9 mmol; 60% dispersion) in dry DMF (50 mL) at 0°C was added a solution of 21-2 (2.0 g, 9.9 mmol) in DMF (15 mL). After 10 min, the cooling bath was removed, but then returned after another 10 min, followed by addition of allyl bromide (4.3 mL, 50 mmol). After 1.5 h, the reaction was quenched with 10% KHSO_4 and then diluted with H_2O (90 mL). The reaction mixture was extracted with EtOAc, the layers separated, and the EtOAc portion washed with H_2O , 5% KHSO_4 , sat. NaHCO_3 and brine, dried (MgSO_4) and concentrated. Flash chromatography (silica, 20% EtOAc/hexanes) gave 21-3 as a yellowish oil. R_f 0.47 (silica, 20% EtOAc/hexanes).

^1H NMR (400 MHz, CDCl_3) δ 5.92 (m, 1H), 5.28 (m, 1H), 5.17 (m, 1H), 4.02 (m, 2H), 3.79 (m, 2H), 3.50 (m, 1H), 3.08 (m, 2H), 1.82 (m, 2H), 1.51 (m, 2H), 1.45 (s, 9H).

2-[(N-Boc-Piperidin-4-yl)oxy]ethanol (21-4)

Ozone was bubbled into a solution of 21-3 (1.5 g, 6.4 mmol) in 2:1 $\text{CH}_3\text{OH}/\text{CH}_2\text{Cl}_2$ (102 mL) at -78°C . After 5 min no starting material remained so oxygen was bubbled through the solution for 15 min to remove excess ozone. NaBH_4 (1.7 g, 45 mmol) was added and the cooling bath removed. After 1 h the reaction mixture was concentrated. The residue was diluted with H_2O (30 mL) and then extracted with CHCl_3 (300 mL). The organic phase was washed with brine (30 mL), dried (MgSO_4), and concentrated. Flash chromatography (silica, EtOAc) gave 21-4 as a nearly colorless oil. R_f 0.42 (silica, EtOAc).

^1H NMR (400 MHz, CDCl_3) δ 3.75 (m, 4H), 3.59 (m, 2H), 3.50 (m, 1H), 3.08 (m, 2H), 1.84 (m, 2H), 1.53 (m, 2H), 1.46 (s, 9H).

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Methyl 4-[2-(N-Boc-Piperidin-4-yloxy)ethyloxy]benzoate (21-5)

A stirring solution of 9-1 (0.80 g, 5.2 mmol), PPh₃ (1.7 g, 6.5 mmol), and THF (20 mL) at ambient temperature was treated dropwise with a solution of 21-4 (1.3 g, 5.2 mmol), DEAD (1.0 mL, 6.5 mmol) and THF (20 mL). After addition was complete the reaction mixture was stirred for 20 hours at ambient temperature. The reaction mixture was then diluted with EtOAc and washed with H₂O, sat. NaHCO₃, 5% KHSO₄ and brine. Drying (MgSO₄), concentration, and then flash chromatography (silica, 30% EtOAc/hexanes) gave 21-5 as a colorless oil. TLC R_f = 0.29 (silica, 30% EtOAc/hexanes); ¹H NMR (300 MHz, CDCl₃) δ 7.99 (d, J = 11 Hz, 2H), 6.93 (d, J = 11 Hz, 2H), 4.17 (m, 2H), 3.88 (s, 3H), 3.82 (m, 2H), 3.78 (m, 2H), 3.56 (m, 1H), 3.10 (m, 2H), 1.85 (m, 2H), 1.55 (m, 2H), 1.46 (s, 9H).

4-[2-(N-Boc-Piperidin-4-yloxy)ethyloxy]benzoic acid (21-6)

A solution of 21-5 (1.6 g, 4.1 mmol), ethanol (41 mL), and 1N NaOH (21 mL) was stirred at ambient temperature for 20 hours. The reaction was then concentrated and the residue dissolved in H₂O and then washed with ether. The aqueous phase was acidified with 5% KHSO₄ and then extracted with EtOAc. The EtOAc portion was washed with 5% KHSO₄ and brine, dried (MgSO₄), and concentrated to furnish 21-6 as a white solid. TLC R_f = 0.68 (silica, acetone); ¹H NMR (300 MHz, CDCl₃) δ 8.05 (d, J = 11 Hz, 2H), 6.95 (d, J = 11 Hz, 2H), 4.18 (m, 2H), 3.85 (m, 2H), 3.78 (m, 2H), 3.57 (m, 1H), 3.12 (m, 2H), 1.85 (m, 2H), 1.55 (m, 4H), 1.46 (s, 9H).

4-[2-(N-Boc-Piperidin-4-yloxy)ethyloxy]benzoyl-2(S)-phenyl-sulfonylamino-β-alanine tert-butyl ester (21-7)

A stirring solution of 21-6 (100 mg, 0.27 mmol), DMF (1.5 mL), NMM (105 μL, 0.96 mmol), 19-2a (86 mg, 0.29 mmol), and HOBT (48 mg, 0.36 mmol) at 0°C was treated with EDC (68 mg, 0.36 mmol) followed by removal of the cooling bath. After 20 h the reaction mixture was diluted with EtOAc and then washed with H₂O,

5% KHSO₄, sat. NaHCO₃ and brine, dried (MgSO₄), and concentrated. Flash chromatography (silica, 65% EtOAc/hexanes) gave 21-7 as an oil. TLF R_f = 0.38 (silica, 65% EtOAc/hexanes);

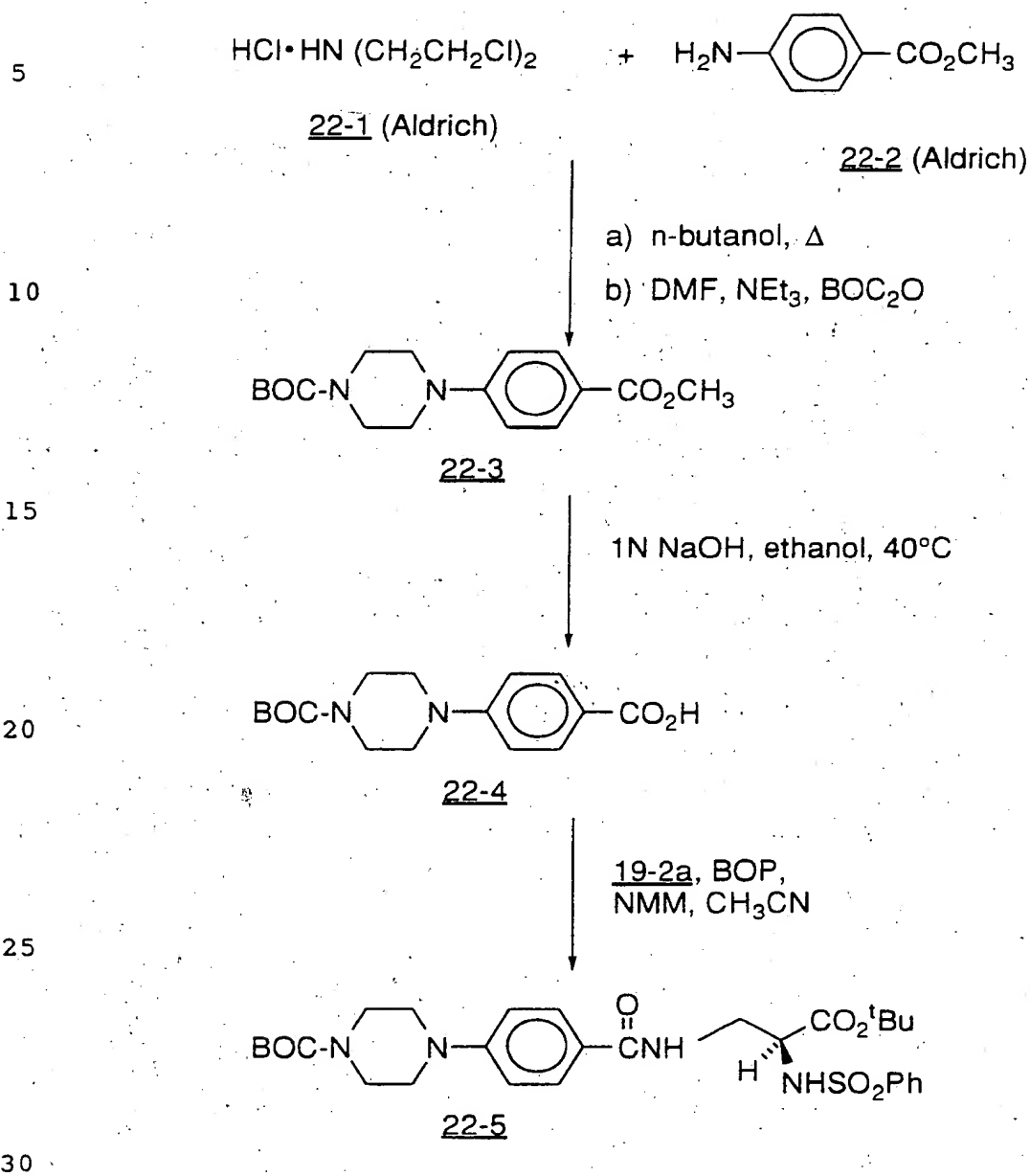
¹H NMR (300 MHz, CDCl₃) δ 7.86 (m, 2H), 7.76 (d, J = 11 Hz, 2H), 7.52 (m, 3H), 6.93 (d, J = 11 Hz, 2H), 6.63 (m, 1H), 5.68 (d, J = 8 Hz, 1H), 4.15 (m, 2H), 3.95-3.70 (m, 6H), 3.55 (m, 2H), 3.10 (m, 2H), 1.85 (m, 2H), 1.57 (m, 2H), 1.45 (s, 9H), 1.28 (s, 9H).

4-[2-(Piperidin-4-yloxy)ethyloxy]benzoyl-2(S)-phenylsulfonylamino-β-alanine (21-8)

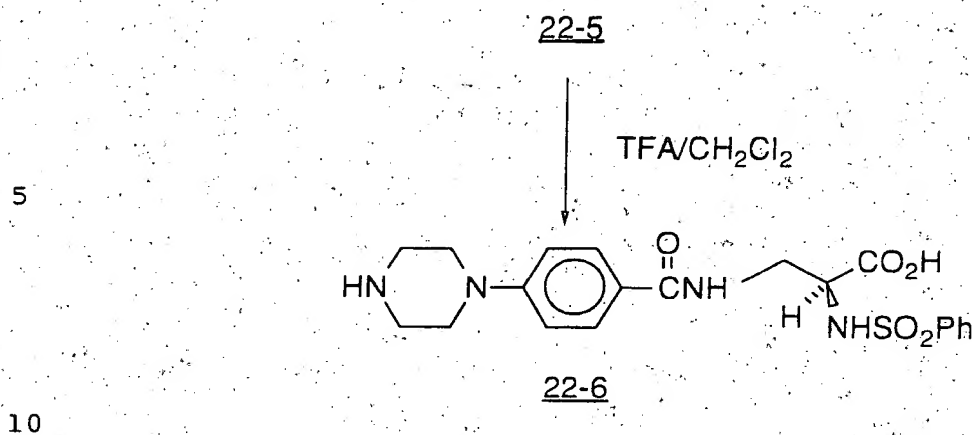
A solution of 21-7 (168 mg, 0.26 mmol), anisole (56 mg, 0.52 mmol), CH₂Cl₂ (1.3 mL), and TFA (1.3 mL) was stirred at ambient temperature for 15 min. Concentration and then flash chromatography (silica, 10:0:0.8 ethanol/NH₄OH/H₂O) gave 21-8 as a white solid. TLC R_f = 0.32 (silica, 10:0.8:0.8 ethanol/NH₄OH/H₂O); R_f 0.46 (silica, 10/0.8/0.8 ethanol/NH₄OH/H₂O)

¹H NMR (400 MHz, D₂O) δ 7.77 (m, 2H), 7.57 (m, 2H), 7.39 (m, 3H), 7.04 (m, 2H), 4.30 (m, 2H), 4.25 (m, 1H), 3.95 (m, 2H), 3.86 (m, 1H), 3.79 (dd, J = 14 and 4 Hz, 1H), 3.48 (dd, J = 16 and 10 Hz, 1H), 3.38 (m, 2H), 3.13 (m, 2H), 2.14 (m, 2H), 1.86 (m, 2H).

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SCHEME 22

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15 Methyl 4-(N-Boc-N'-piperazinyl)benzoate (22-3)

A mixture of 22-1 (2.4 g, 13.2 mmol), 22-2 (2.0 g, 13.2 mmol), and n-butanol (6.5 mL) was refluxed for 5 days. The cooled reaction mixture was then filtered to give the crude phenylpiperazine as a white solid. The crude solid was dissolved in DMF and treated with diisopropylethylamine (2.1 mL, 40 mmol) and Boc₂O (1.6 g, 20 mmol). After 1.0 h the reaction mixture was diluted with EtOAc and then washed with H₂O, sat. NaHCO₃, 10% KHSO₄ and brine, dried (MgSO₄), and concentrated. Flash chromatography (silica, 10% EtOAc/hexanes) gave 22-3 as a white solid. TLC R_f = 0.34 (silica, 20% EtOAc/hexanes);

20 ¹H NMR (300 MHz, CD₃OD) 7.90 (d, J = 11 Hz, 2H), 6.96 (d, J = 11 Hz, 2H), 3.87 (s, 9H), 3.60 (m, 4H), 3.33 (m, 4H), 1.50 (s, 9H).

25 4-(N-Boc-N'-piperazinyl)benzoic acid (22-4)

A mixture of 22-3 (700 mg, 2.2 mmol), 1N NaOH, and ethanol (10 mL) was heated at 40°C for 4 hours. The cooled reaction mixture was acidified with 10% KHSO₄ and then extracted with EtOAc.

30 The organic portion was washed with brine, dried (MgSO₄) and concentrated to give 22-4 as a white solid. TLC R_f = 0.80 (silica, 10:0.5:0.5 CH₂Cl₂/CH₃OH/AcOH);

¹H NMR (400 MHz, CD₃OD) δ 7.92 (d, J = 11 Hz, 2H), 7.01 (d, J = 11 Hz, 2H), 3.62 (m, 4H), 3.34 (m, 4H), 1.52 (s, 9H).

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4-(N-Boc-N'-Piperazinyl)benzoyl-2(S)-phenylsulfonylamino- β -alanine
tert-butyl ester (22-5)

5 A mixture of 22-4 (300 mg, 1.0 mmol), 19-2a (329 mg, 1.0 mmol), NMM (430 μ L, 4.0 mmol), and CH₃CN (5 mL) at ambient temperature was treated with BOP (650 mg, 1.5 mmol). After 20 h the reaction mixture was diluted with EtOAc and then washed with 10% KHSO₄ and brine, dried (MgSO₄) and concentrated. Flash chromatography (silica, 40% EtOAc/hexanes) gave 22-5 as a white solid. TLC R_f = 0.16 (silica, 40% EtOAc/hexanes);
10 ¹H NMR (300 MHz, CD₃OD) δ 7.75 (m, 2H), 7.60 (d, J = 11 Hz, 2H), 7.40 (m, 3H), 6.88 (d, J = 11 Hz, 2H), 4.03 (m, 1H), 3.50 (m, 4H), 3.30 (m, 6H), 1.44 (s, 9H), 1.16 (s, 9H).

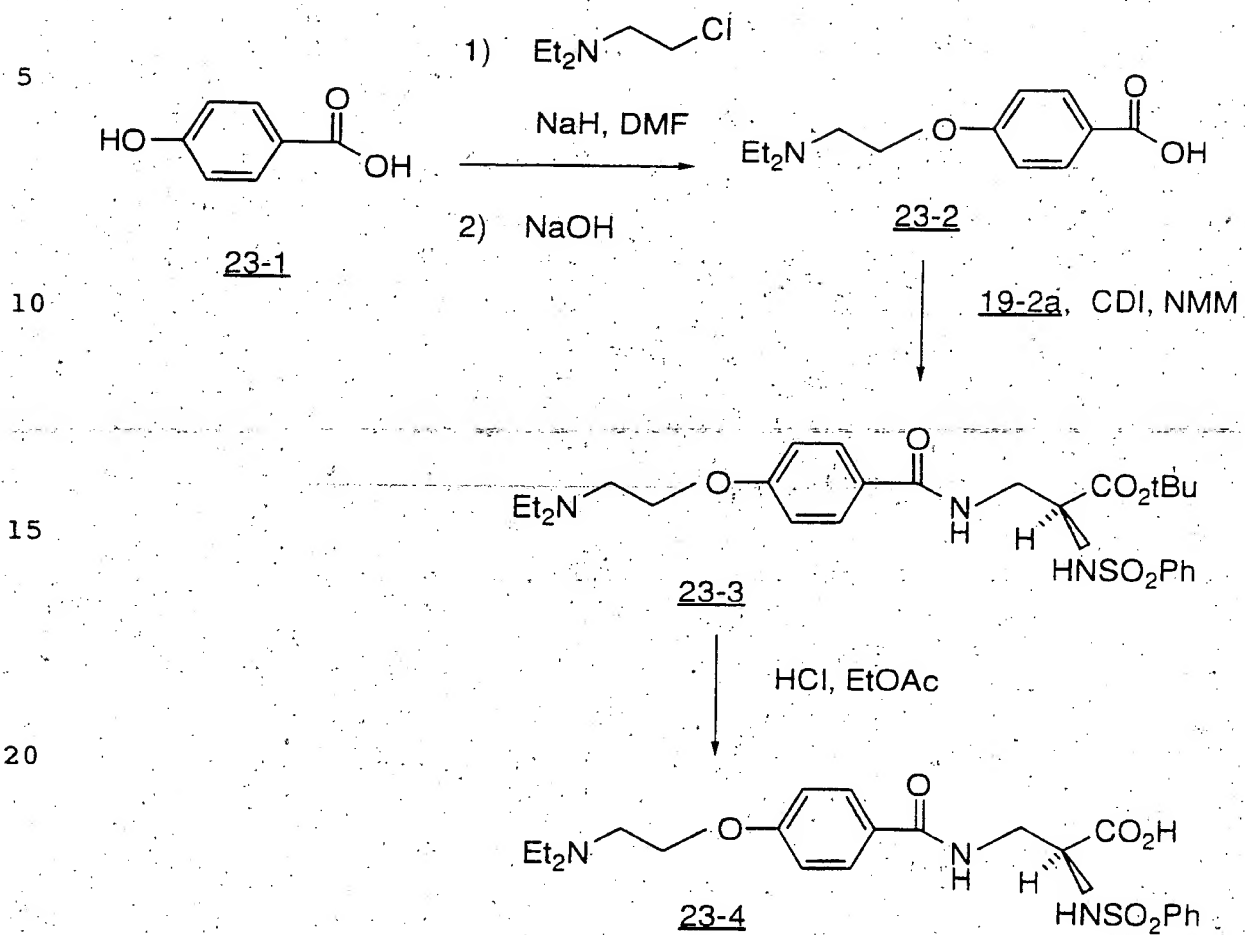
4-(N-Piperazinyl)benzoyl-2(S)-phenylsulfonylamino- β -alanine (22-6)

15 A solution of 22-5 (300 mg, 0.51 mmol), TFA (4 mL), and CH₂Cl₂ (4 mL) was stirred at ambient temperature for 3.0 hours. The solution was then concentrated followed by azeotropic removal of residual TFA with toluene. The residue was triturated with (10:1:1 ethanol/NH₄OH/H₂O), filtered, and dried in vacuo to give 22-5 as a white solid. TLC R_f = 0.37 (silica, ethanol/NH₄OH/H₂O 10:1:1).
20 ¹H NMR (400 MHz, CD₃OD) δ 7.85 (m, 2H), 7.77 (d, J = 11 Hz, 2H), 7.50 (m, 3H), 7.20 (d, J = 11 Hz, 2H), 4.26 (m, 1H), 3.80-3.45 (m, 10H).

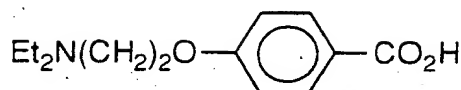
25

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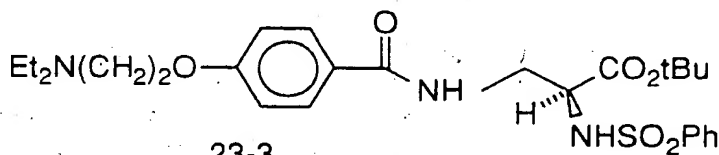
SCHEME 23

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23-24-[2-(N,N-Diethylamino)ethoxy]benzoic acid (23-2)

A solution of 4-hydroxybenzoic acid (Aldrich) (10 g, 72 mmol) in DMF (100 mL) was treated with NaH (50% dispersion in oil, 10.4 g, 216 mmol) and N,N-diethylchloroethylamine•HCl (Aldrich) (12.5 g, 72 mmol) at room temperature for 24 h. The solution was concentrated, the residue was dissolved in water, acidified to pH2, and extracted with 4x 100 mL EtOAc. The organic layers were concentrated to give the bis-alkylated product as a white solid which was dissolved in water (30 mL) and dioxane (50 mL) and treated with 5.4 g NaOH. After 24 h the solution was concentrated and the residue was chromatographed (40:1:1 EtOH/H₂O/NH₄OH) to give 23-2 as a white solid. R_f (40:1:1 EtOH/H₂O/NH₄OH) 0.24

¹H NMR (300 MHz, D₂O) δ 7.9 (d, 2H), 7.0 (d, 2H), 4.35 (m, 2H), 3.50 (m, 2H), 3.22 (m, 4H), 1.35 (m, 6H).

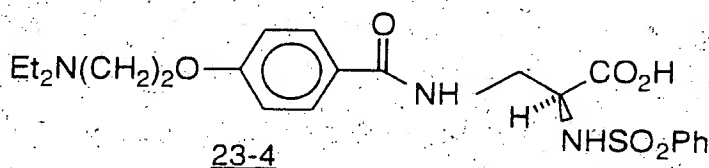
23-34-[2-(N,N-Diethylamino)ethoxy]benzoyl-2(S)-phenylsulfonylamino-β-alanine t-butyl ester (23-3)

A solution of 23-2 (0.6 g, 2.5 mmol) in DMF (10 mL) was treated with carbonyldiimidazole (0.49 g, 3 mmol) for 30 minutes, followed by 9-12 (0.85 g, 2.5 mmol) and N-methylmorpholine (0.84 mL, 7.6 mmol). The solution was stirred at room temperature for 24 h, then concentrated, adsorbed to silica and chromatographed (80%

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acetone/hexanes) to give 23-3 as a white solid. R_f (80% acetone/hexanes) 0.37

1H NMR (300-MHz, $CDCl_3$) δ 7.82 (d, 2H), 7.7 (m, 4H), 7.5 (d, 1H), 7.41 (d, 2H), 6.8 (d, 2H), 4.08 (m, 3H), 3.78 (m, 2H), 2.9 (t, 2H), 2.65 (q, 4H), 1.25 (s, 9H), 1.4 (t, 6H).



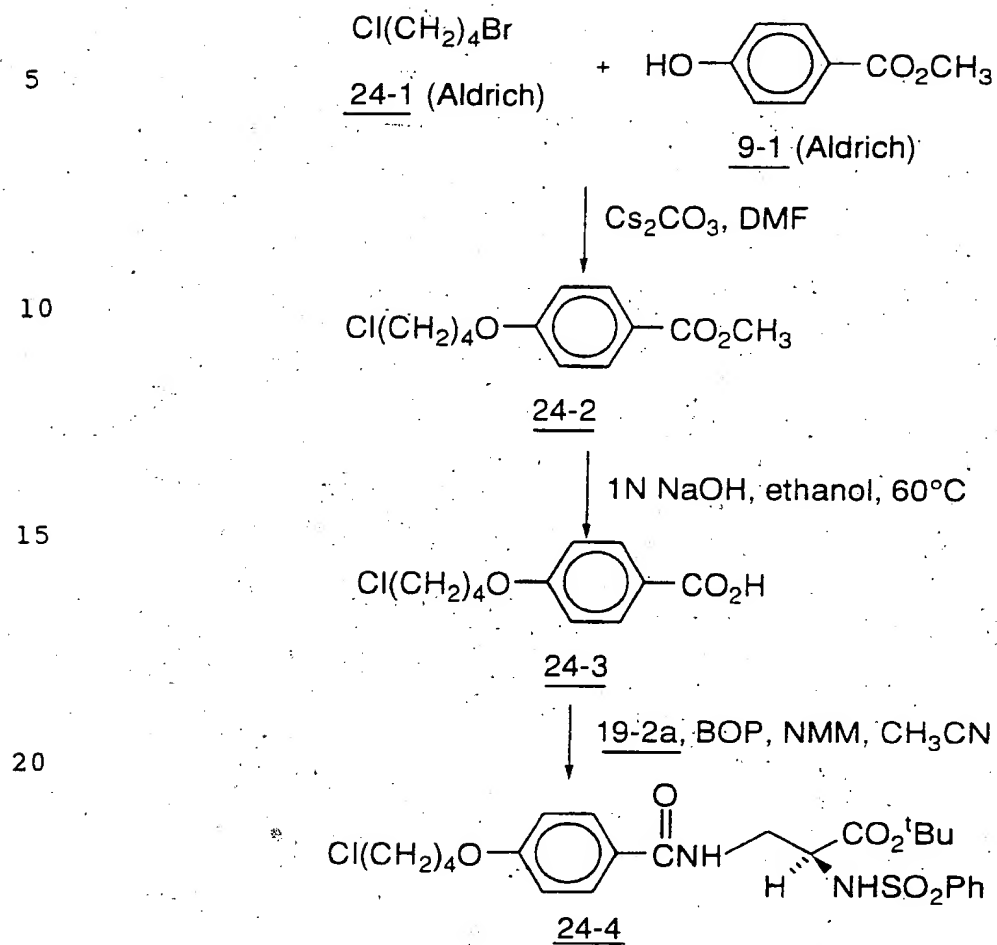
4-[2-(N,N-Diethylamino)ethoxy]benzoyl-2(S)-phenylsulfonylamino- β -alanine (23-4)

A solution of 23-3 in EtOAc (10 mL) was cooled to $-78^\circ C$, saturated with HCl gas and warmed to $0^\circ C$ for 1 h. The solution was concentrated and the residue was purified by preparative HPLC to give 23-4 as a white solid (TFA salt).

1H NMR (300 MHz, D_2O) δ 7.72 (d, 2H), 7.55 (d, 2H), 7.35 (m, 3H), 7.0 (d, 2H), 4.20 (bs, 2H), 4.16 (dd, 1H), 3.72 (dd, 1H), 3.6 (bs, 2H), 3.4 (dd, 1H), 3.14 (m, 4H), 1.3 (m, 6H).

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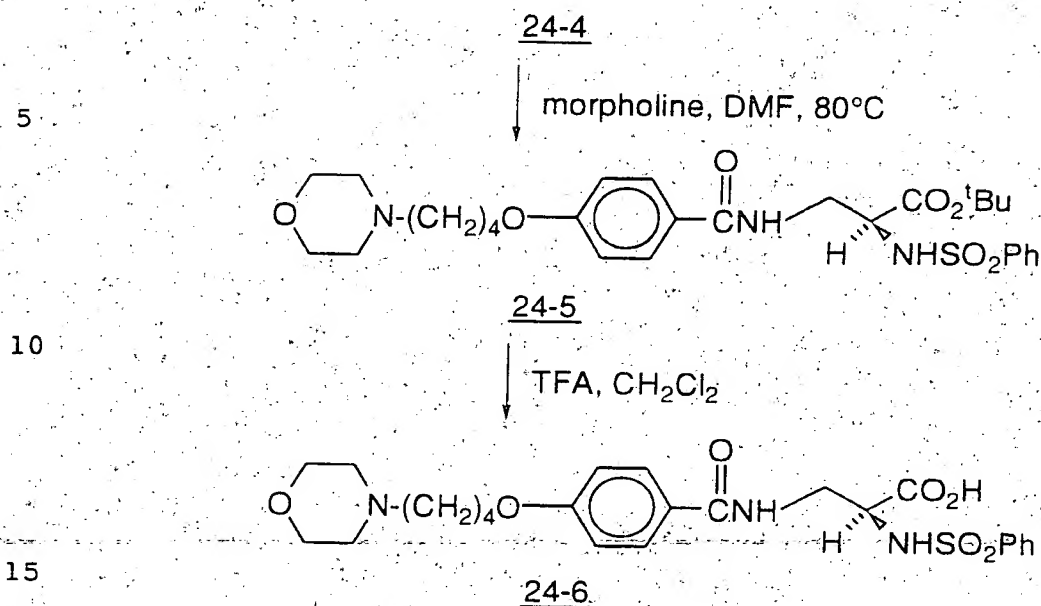
SCHEME 24



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SCHEME 24 CONT'D



Methyl 4-(4-Chlorobutyloxy)benzoate (24-2)

A stirring solution of 9-1 (2.0 g, 13.1 mmol), 24-1 (4.5 g, 26.2 mmol) and DMF at ambient temperature was treated with Cs₂CO₃ (6.4 g, 20 mmol). After 1.0 hour the reaction mixture was diluted with EtOAc and then washed with H₂O, 10% KHSO₄ and brine, dried (MgSO₄), and concentrated. Flash chromatography (silica, 10% EtOAc/hexanes) gave 24-2 as a colorless oil. TLC R_f=0.58 (silica, 20% EtOAc/hexanes);

20

25

¹H NMR (300 MHz, CDCl₃) δ 7.99 (d, J=11Hz, 2H), 6.90 (d, J= 11Hz, 2H), 4.06 (m, 2H), 3.89 (s, 3H), 3.62 (m, 2H), 1.98 (m, 2H).

4-(4-Chlorobutyloxy)benzoic acid (24-3)

A mixture of 24-2 (3.0 g, 12.4 mmol), 1N NaOH (30 mL), and ethanol was heated at 60°C for 1.0 hour. The cooled reaction mixture was acidified with 10% KHSO₄ and then extracted with EtOAc. The EtOAc portion was washed with brine, dried (MgSO₄) and concentrated to give 24-3 as a white solid.

30

¹H NMR (300 MHz, CD₃OD) δ 7.98 (d, J = 11Hz, 2H), 6.98 (d, J = 11Hz, 2H), 4.07 (m, 2H), 3.63 (m, 2H), 1.94 (m, 4H).

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4-(4-Chlorobutyloxy)benzoyl-2(S)-phenylsulfonylamino- β -alanine tert-butylester (24-4)

5 A stirring solution of 24-3 (250 mg, 1.1 mmol), 19-2a (368 mg, 1.1 mmol), NMM (442 mg, 4.4 mmol), and CH₃CN (5 mL) at ambient temperature was treated with BOP (483 mg, 1.1 mmol). After 20 h the reaction mixture was diluted with EtOAc and then washed with H₂O, sat. NaHCO₃, 10% KHSO₄ and brine, dried (MgSO₄) and concentrated. Flash chromatography (silica, 40% EtOAc/hexanes) gave 24-4 as a white solid. TLC R_f = 0.46 (silica, 50% EtOAc/hexanes); ¹H NMR (300 MHz, 10% CD₃OD/CDCl₃) δ 7.85 (m, 2H), 7.76 (d, J = 11 Hz, 2H), 7.52 (m, 3H), 6.92 (d, J = 11 Hz, 2H), 4.06 (m, 2H), 3.99 (m, 1H), 3.82-3.60 (m, 4H), 1.99 (m, 4H), 1.26 (s, 9H).

15 4-[4(N-Morpholino)butyloxy]benzoyl]-2(S)-phenylsulfonylamino- β -alanine tert-butyl ester (24-5)

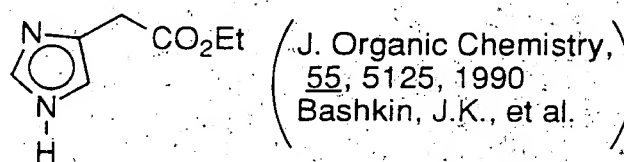
A stirring solution of 24-4 (500 mg, 1.0 mmol), morpholine (437 μ L, 5.0 mmol), and DMF (5 mL) was heated at 80°C for 20 hours. The cooled reaction mixture was diluted with EtOAc and then washed with H₂O and brine, dried (MgSO₄) and concentrated. Flash chromatography (silica, EtOAc) gave 24-5 as a yellow solid. TLC R_f 0.14 (silica, EtOAc); ¹H NMR (300 MHz, CD₃OD) δ 7.83 (m, 2H), 7.74 (d, J = 11 Hz, 2H), 7.50 (m, 3H), 6.96 (d, J = 11 Hz, 2H), 4.10 (m, 3H), 3.73-3.40 (m, 8H), 2.45 (m, 4H), 1.90-1.65 (m, 4H), 1.26 (s, 9H).

4-[4-(N-Morpholino)butyloxy]benzoyl-2(S)-phenylsulfonylamino- β -alanine (24-6)

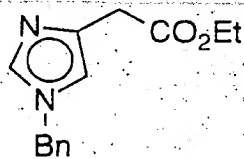
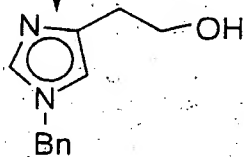
30 A solution of 24-5 (430 mg, 0.76 mmol), TFA (5 mL), and CH₂Cl₂ (5 mL) was stirred at ambient temperature for 3.0 hours. Concentration of the reaction mixture followed by azeotropic removal of residual TFA with toluene gave crude 24-6. Flash chromatography (silica, 10:0.1:0.1 ethanol/H₂O/NH₄OH) gave 24-6 as a white solid. TLC R_f = 0.52 (silica, 10:0.1:0.1 ethanol/NH₄OH/H₂O);

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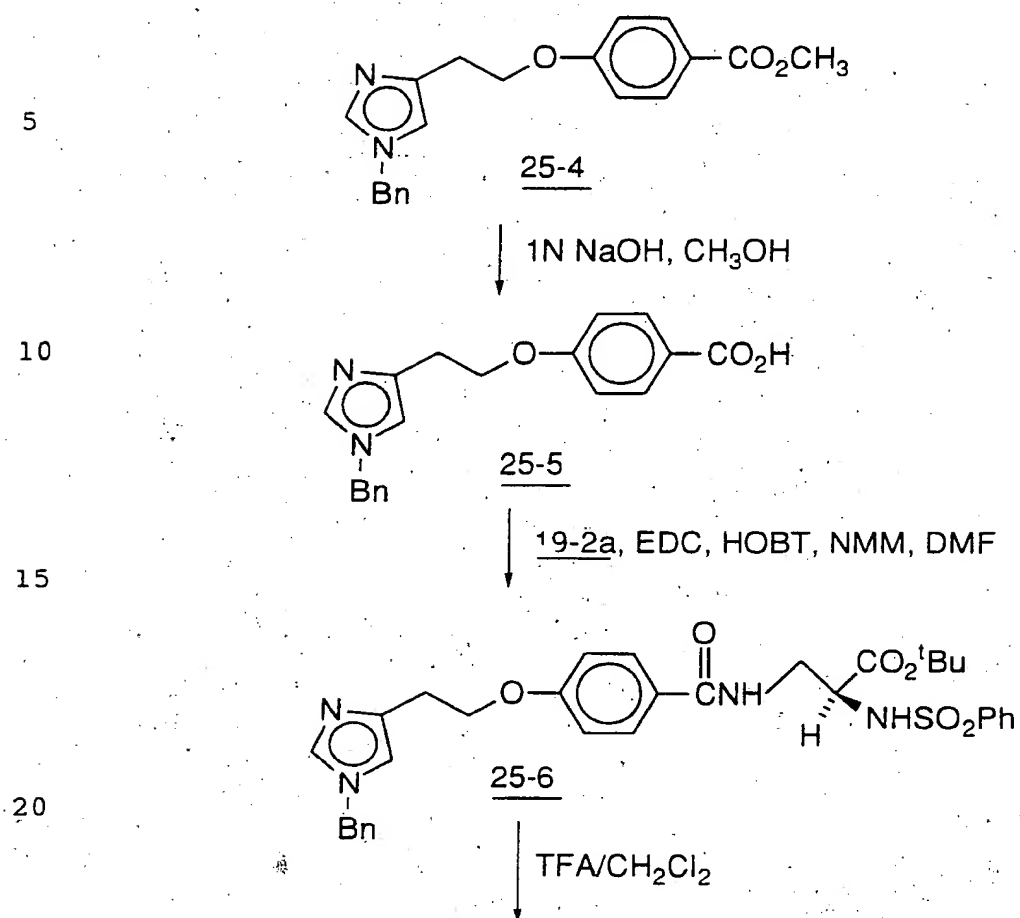
^1H NMR (400 MHz, D_2O) δ 7.68 (d, $J = 10$ Hz, 2H), 7.48 (d, $J = 11$ Hz, 2H), 7.30 (m, 3H), 6.96 (d, $J = 11$ Hz, 2H), 4.08 (m, 3H), 4.00-3.00 (m, 10H), 1.80 (m, 4H).

SCHEME 2525-1

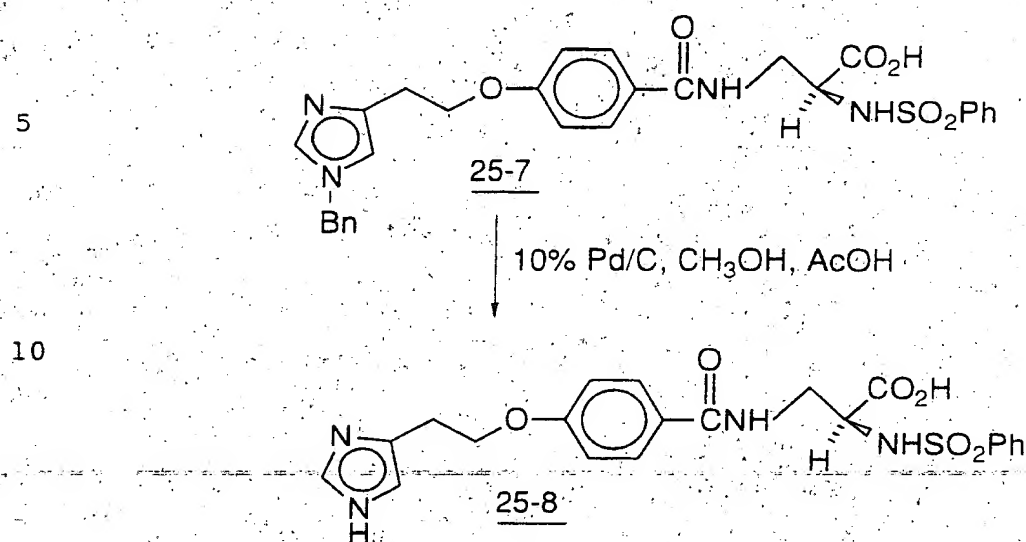
NaH, THF, benzyl bromide

25-2THF, LiAlH_4 25-39-1, Ph_3P , DIAD, THF

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SCHEME 25 CONT'D

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SCHEME 25 CONT'DEthyl (N-Benzylimidazol-4-yl)acetate (25-2)

To a magnetically stirred suspension of NaH (1.1 g, 26 mmol) in THF (25°C) at 0°C was added 25-1 (3.8 g, 24.6 mmol) in THF (15 mL) dropwise over 30 min., followed by removal of the cooling bath. After 3 hours benzyl bromide (2.8 mL, 23.4 mmol) added. After 20 hours the mixture was diluted with CH₂Cl₂ and then washed with H₂O, dried (MgSO₄) and concentrated. Flash chromatography (silica, 40% (CHCl₃/NH₃)/EtOAc) gave 25-2 as a pale yellow liquid. TLC R_f = 0.15 (silica, 40% (CHCl₃/NH₃)/EtOAc);

¹H NMR (300 MHz, CDCl₃) δ 7.47 (s, 1H), 7.40-7.15 (m, 5H), 6.87 (s, 1H), 5.07 (s, 2H), 4.26 (q, J = 7 Hz, 2H), 3.63 (s, 2H), 1.26 (t, J = 7 Hz, 3H).

(N-Benzylimidazol-4-yl)ethanol (25-3)

A solution of 25-2 (4.6 g, 18.8 mmol) in THF (50 mL) at ambient temperature was treated dropwise with LiAlH₄ (9.4 mL, 9.4 mmol, 1M in THF). After stirring for 1 hour the reaction was quenched with a saturated sodium potassium tartrate solution. The mixture was then poured into EtOAc and washed with H₂O and brine, dried (MgSO₄) and concentrated to yield 25-3 as a yellow oil.

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¹H NMR (300 MHz, CDCl₃) δ 7.45 (s, 1H), 7.40-7.10 (m, 5H), 6.68 (s, 1H), 5.03 (s, 2H), 3.88 (t, J = 6 Hz, 2H), 2.78 (t, J = 6 Hz, 2H).

5 Methyl 4-(2-(N-Benzylimidazol-4-yl)ethyloxy)benzoate (25-4).

A stirring solution of 9-1 (152 mg, 1.0 mmol), PPh₃ (341 mg, 1.3 mmol), and THF (20 mL) at ambient temperature was treated dropwise with DIAD (256 μL, 1.3 mmol), 25-3 (202 mg, 1.0 mmol), and THF (10 mL) over 30 min followed by heating at 70°C for 24 hours. The cooled reaction mixture was concentrated and then chromatographed (silica, 40% (CHCl₃/NH₃)/EtOAc) to give 25-4 as a colorless gum. TLC R_f = 0.16 (silica, 40% (CHCl₃/NH₃/EtOAc); ¹H NMR (300 MHz, CDCl₃) δ 7.96 (d, J = 11 Hz, 2H), 7.48 (s, 1H), 7.40-7.10 (m, 5H), 6.90 (d, J = 11 Hz, 2H), 6.74 (s, 1H), 5.05 (s, 2H), 4.28 (t, J = 7 Hz, 2H), 3.85 (s, 3H), 3.06 (t, J = 7 Hz, 2H).

15 4-[2-(N-Benzylimidazol-4-yl)ethyloxy]benzoic acid (25-5)

A mixture of the ester 25-4 (170 mg, 0.51 mmol), CH₃OH (10 mL), and 1N NaOH (5 mL) was stirred for 20 hours at ambient temperature. The cooled reaction mixture was acidified with 1N HCl (5 mL) and extracted with EtOAc. The EtOAc portion was concentrated to give 25-5 as a gelataneous solid. ¹H NMR (300 MHz, CD₃OD) δ 7.90 (d, J = 11 Hz, 2H), 7.67 (s, 1H), 7.40-7.20 (m, 5H), 6.95 (s, 1H), 6.88 (d, J = 11 Hz, 2H), 4.23 (t, J = 6 Hz, 2H), 2.98 (t, J = 6 Hz, 2H).

25 4-[2-(N-Benzylimidazol-4-yl)ethyloxy]benzoyl-2(S)-phenylsulfonyl-amino-β-alanine tert-butyl ester (25-6)

A stirring solution of 25-5 (147 mg, 0.46 mmol), 19-2a (154 mg, 0.46 mmol), HOBT (94 mg, 0.62 mmol), NMM (100 μL, 0.91 mmol), and DMF (120 mL) at 0°C was treated with EDC (118 mg, 0.62 mmol) and the cooling bath removed. After 24 hours the reaction mixture was concentrated. Flash chromatography (silica, CH₂Cl₂, CH₃OH/AcOH 9:0.5:0.5) gave 25-6 as a pale yellow solid. TLC R_f = 0.35 (silica, 8:1:1 CH₂Cl₂/CH₃OH/AcOH);

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¹H NMR (300 MHz, CDCl₃) δ 7.87 (m, 2H), 7.73 (d, J = 11 Hz, 2H), 7.60-7.10 (m, 6H), 6.92 (d, J = 11 Hz, 2H), 6.75 (s, 1H), 6.59 (m, 1H), 5.67 (m, 1H), 5.07 (s, 2H), 4.27 (t, J = 6 Hz, 2H), 3.90 (m, 2H), 3.56 (m, 1H), 3.05 (t, J = 6 Hz, 2H), 1.28 (s, 9H).

4-[2-(N-Benzylimidazol-4-yl)ethyloxy]benzoyl-2(S)-phenylsulfonyl-amino-β-alanine (25-7)

Utilizing the procedure for converting 24-5 to 24-6, 25-6 (252 mg, 0.42 mmol) gave 25-7 as a colorless solid after chromatography (silica, ethanol/NH₄OH/H₂O, 9:0.5:0.5).

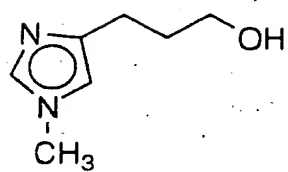
¹H NMR (300 MHz, CD₃OD) δ 7.99 (s, 1H), 7.84 (m, 2H), 7.73 (d, J = 11 Hz, 2H), 7.55-7.25 (m, 8H), 7.08 (s, 1H), 6.93 (d, J = 11 Hz, 2H), 5.22 (s, 2H), 4.23 (t, J = 6 Hz, 2H), 3.90-3.50 (m, 3H), 3.04 (t, J = 6 Hz, 2H).

4-[2-(Imidazol-4-ylethyloxy)benzoyl-2(S)-phenylsulfonylamino-β-alanine (25-8)

A mixture of 25-7 (94 mg, 0.17 mmol), 10% Pd/C (94 mg), and 4% formic acid/CH₃OH (50 mL) was stirred under a hydrogen atmosphere at ambient temperature for 4 days. Filtration, concentration of the filtrate, and the flash chromatography (silica, 10:1:1 ethanol/H₂O/NH₄OH) gave 25-7 as a solid. TLC R_f = 0.31 (silica, 10:1:1 ethanol/NH₄OH/H₂O);

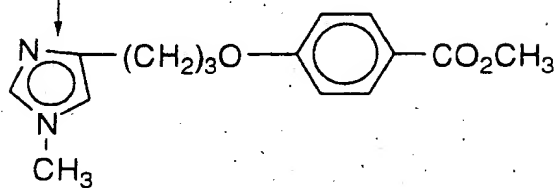
¹H NMR (400 MHz, CD₃OD) δ 7.86 (m, 3H), 7.77 (d, J = 11 Hz, 2H), 7.50 (m, 3H), 7.03 (s, 1H), 6.98 (d, J = 11 Hz, 2H), 4.28 (t, J = 6 Hz, 2H), 3.80-3.50 (m, 3H), 3.12 (t, J = 11 Hz, 2H).

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SCHEME 26

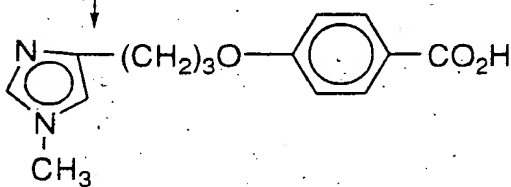
10

↓ 9-1, Ph₃P, DIAD, THF



15

↓ 1N NaOH, CH₃OH

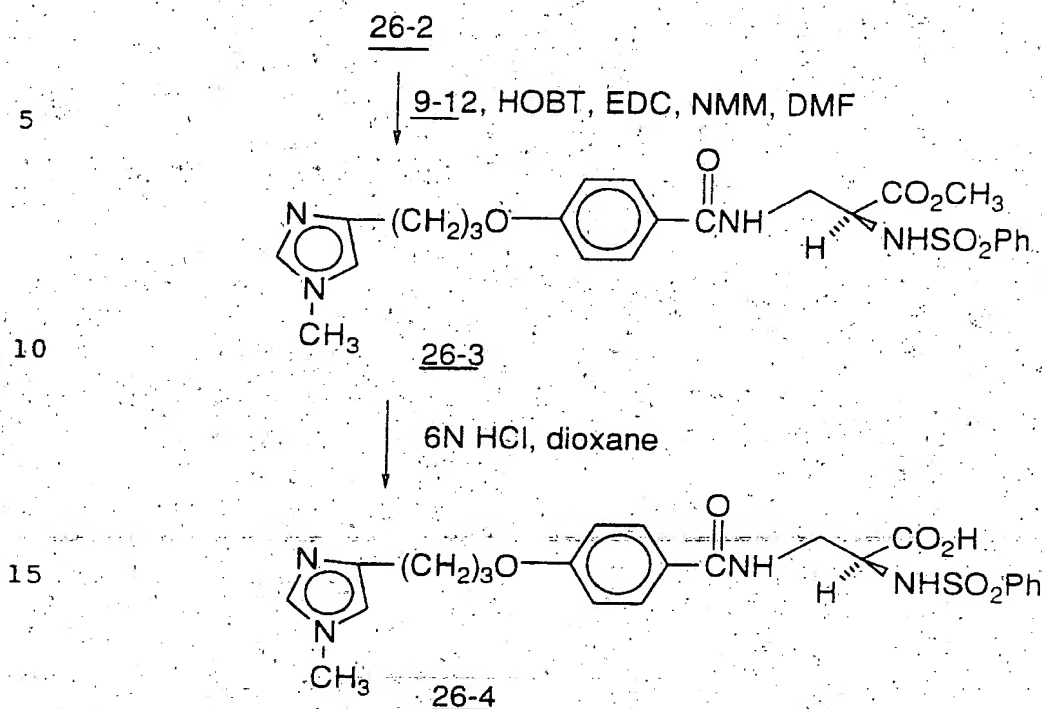


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SCHEME 26 CONT'D

Methyl 4-[3-(1-Methylimidazol-4-yl)propoxy]benzoate (26-1)

Utilizing the procedure for converting 25-3 to 25-4, 35-5 (743 mg, 4.9 mmol) was converted to 26-1 after flash chromatography (silica, 40% (CHCl₃/NH₃)/EtOAc). TLC R_f = 0.15 (silica, 40% (CHCl₃/NH₃)/EtOAc);

¹H NMR (300 MHz, CDCl₃) δ 7.99 (d, J = 11 Hz, 2H), 7.33 (s, 1H), 6.91 (d, J = 11 Hz, 2H), 6.62 (s, 1H), 4.05 (t, J = 6 Hz, 2H), 3.88 (s, 3H), 3.62 (s, 3H), 2.76 (t, J = 6 Hz, 2H), 2.16 (m, 2H).

4-[3-(1-Methylimidazol-4-yl)propoxy]benzoic acid (26-2)

Utilizing the procedure for converting 25-4 to 25-5, 26-1 (420 mg, 1.5 mmol) furnished 26-2 as a colorless solid.

¹H NMR (300 MHz, CD₃OD) δ 8.77 (s, 1H), 7.97 (d, J = 11 Hz, 2H), 7.35 (s, 1H), 6.96 (d, J = 11 Hz, 2H), 4.13 (t, J = 6 Hz, 2H), 3.88 (s, 3H), 2.93 (m, 2H), 2.17 (m, 2H).

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4-[3-(1-Methylimidazol-4-yl)propyloxy]benzoyl-2(S)-
phenylsulfonylamino- β -alanine methyl ester (26-3)

Utilizing the procedure for coupling 25-5 and 19-2a to
furnish 25-6, 26-2 (310 mg, 1.2 mmol) was coupled to 9-12 (351 mg,
1.2 mmol) to afford 26-3 as a cream-colored solid after flash
chromatography (silica, 95% (CHCl₃/NH₃)/CH₃OH); TLC R_f = 0.21
(silica, 95% (CHCl₃/NH₃)/CH₃OH);

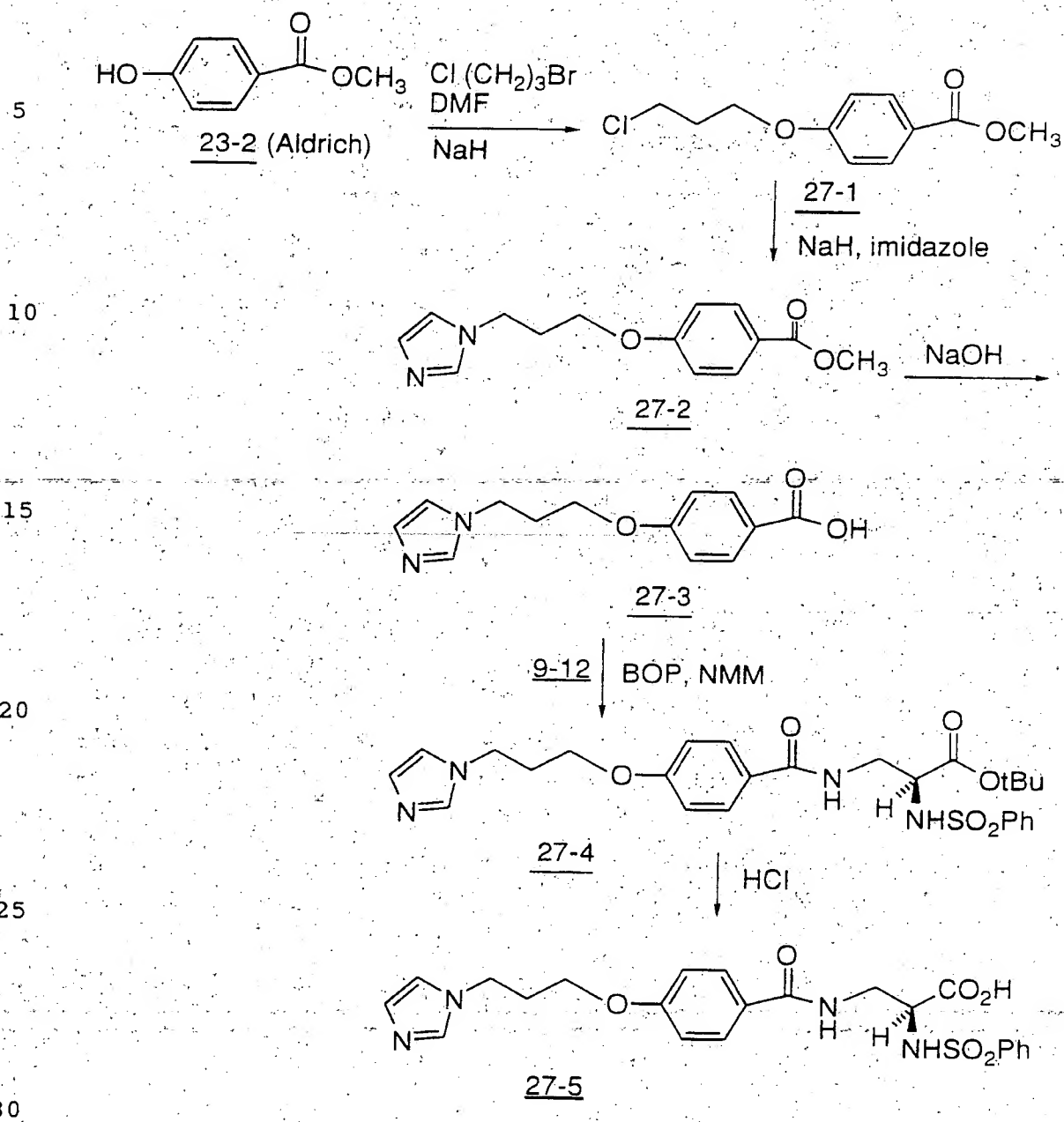
¹H NMR (300 MHz, CDCl₃) δ 7.82 (m, 2H), 7.69 (d, J = 11 Hz, 2H),
7.50 (m, 3H), 7.36 (s, 1H), 7.02 (m, 1H), 6.84 (d, J = 11 Hz, 2H), 6.62
(s, 1H), 4.13 (m, 1H), 4.00 (t, J = 6 Hz, 2H), 3.85-3.60 (m, 2H), 3.62 (s,
3H), 3.57 (s, 3H), 2.72 (m, 2H), 2.13 (m, 2H).

4-[3-(1-Methylimidazol-4-yl)propyloxy]benzoyl-2(S)-phenylsulfonyl-
amino- β -alanine (26-4)

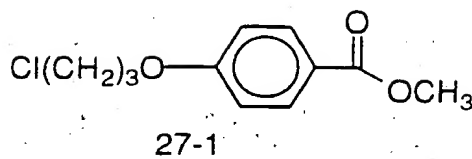
A solution of 26-3 (560 mg, 1.1 mmol), dioxane (25 mL),
and 1N HCl (25 mL) was stirred for 24 hours at ambient temperature.
Concentration and then flash chromatography (silica, ethanol/-
NH₄OH)H₂O 9:0.5:0.5) gave 26-4 as a solid. TLC R_f = 0.29 silica,
9:0.5:0.5 ethanol/-NH₄OH)H₂O.

¹H NMR (300 MHz, CD₃OD) δ 8.11 (s, 1H), 7.85 (m, 2H), 7.74 (d, J =
11 Hz, 2H), 7.50 (m, 3H), 7.06 (s, 1H), 5.93 (d, J = 11 Hz, 2H), 4.07 (t,
J = 6 Hz, 2H), 3.90-3.50 (m, 3H), 3.75 (s, 3H), 2.80 (m, 2H), 2.13 (m,
2H).

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SCHEME 27

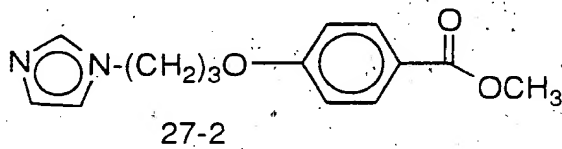
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Methyl 4-[(3-chloropropyl)oxy]benzoate (27-1)

A solution of Methyl 4-hydroxy benzoic acid (23-2) (Aldrich) (4.56 g, 30 mmol) in DMF (100 mL) was treated with Cs₂CO₃ (14.67 g, 45 mmol) at room temperature. After 0.5 hours, 3-bromo-1-chloropropane (5.94 mL, 60 mmol) was added and the solution was stirred for 4 hours. The reaction mixture was filtered and concentrated to give 27-1 as a white solid. R_f (10% EtOAc/hexanes) 0.36.

¹H NMR (400 MHz, CDCl₃) δ 8.0 (d, 2H), 6.9 (d, 2H), 4.17 (t, 2H), 3.88 (s, 3H), 3.75 (t, 2H), 2.26 (m, 2H).

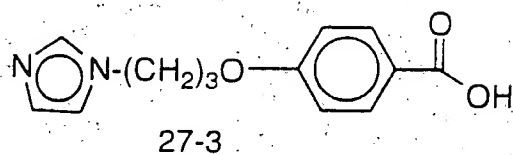


Methyl 4-[3-(1-imidazolyl)propyloxy]benzoate (27-2)

A solution of imidazole (2.38 g, 34.6 mmol) in DMF (30 mL) was treated with NaH (1.38 g, 34.6 mmol, 60% dispersion) and the mixture was heated to 100°C for 20 minutes. A solution of 27-1 (7.5 g, 34.6 mmol) in 5 mL DMF was added and the reaction was heated (100°C) for 5 hours. The solvent was removed *in vacuo* and the residue was dissolved in water and extracted with CHCl₃. The organic layers were washed with water, dried (Na₂SO₄), concentrated, and chromatographed using a gradient (CHCl₃—>3% CH₃OH/CHCl₃). The compound was further purified by medium pressure HPLC to give 27-2 as a yellow oil. R_f (3% CH₃OH/CHCl₃) 0.10.

¹H NMR (300 MHz, CDCl₃) δ 8.0 (d, 2H), 7.99 (s, 1H), 7.08 (s, 1H), 6.90 (m, 3H), 4.2 (t, 2H), 3.96 (t, 2H), 3.90 (s, 3H), 2.26 (m, 2H).

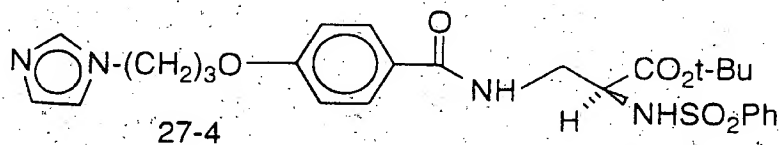
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5 4-[3-(1-Imidazolyl)propyloxy]benzoic acid (27-3)

A solution of 27-2 (5.0 g, 19.2 mmol) in EtOH (100 mL) was treated with 1N NaOH (20.2 mL) for 20 hours. The solution was concentrated and 27-3 was used without further purification. R_f (9:1:1 CHCl₃/CH₃OH/HOAc) 0.27.

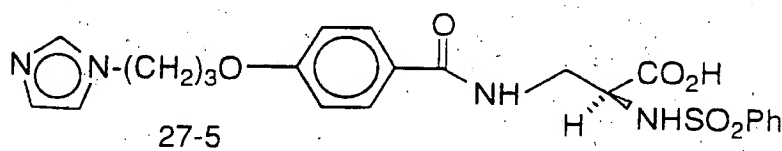
10 ¹H NMR (400 MHz, DMSO) δ 7.82 (d, 2H), 7.62 (s, 1H), 7.20 (s, 1H), 6.88 (s, 1H), 6.83 (d, 2H), 4.14 (t, 2H), 3.90 (t, 2H), 2.18 (m, 2H).



15 4-[3-(1-Imidazolyl)propyloxy]benzoyl-2(S)-phenylsulfonylamino-β-alanine t-butyl ester (27-4)

20 A solution of 27-3 (0.6 g, 2.44 mmol) in CH₃CN (20 mL) was treated with 9-12 (0.74 g, 2.44 mmol), BOP reagent (1.08 g, 2.44 mmol) and N-methylmorpholine (1.2 mL, 11 mmol) at room temperature for 24 hours. The reaction was concentrated and chromatographed (5% CH₃OH/CHCl₃ saturated with NH₃) to give 27-4 as a colorless oil. R_f (10% CH₃OH/CHCl₃ saturated with NH₃) 0.59.

25 ¹H NMR (300 MHz, CDCl₃) δ 7.90 (d, 2H), 7.82 (d, 2H), 7.6 (m, 1H), 7.55 (m, 3H), 7.1 (s, 1H), 6.95 (m, 3H), 6.7 (m, 1H), 5.75 (m, 1H), 4.24 (t, 2H), 4.0 (t, 2H), 3.93 (m, 2H), 3.6 (m, 1H), 2.3 (m, 2H), 1.34 (s, 9H).

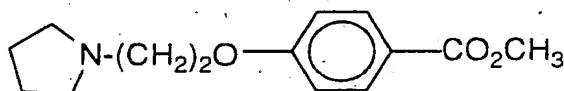


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4-[3-(1-Imidazolyl)propyloxy]benzoyl-2(S)-phenylsulfonylamino- β -alanine (27-5)

A solution of 27-4 (1.2 g, 2.27 mmol) in EtOAc (15 mL) was cooled to -78°C and saturated with HCl gas. This solution was warmed to 0°C for 1.5 hours, degassed with argon and concentrated to give a colorless oil, which was chromatographed (10:0.5:0.5 EtOH/H₂O/NH₄OH) to give 27-5 as a white solid.

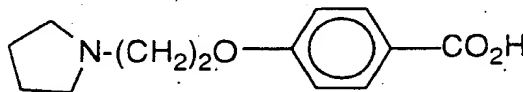
¹H NMR (CD₃OD) δ 8.32 (s, 1H), 7.84 (d, 2H), 7.78 (d, 2H), 7.52 (m, 1H), 7.46 (m, 3H), 7.28 (s, 1H), 6.94 (d, 2H), 4.38 (t, 2H), 4.06 (t, 2H), 3.93 (dd, 1H), 3.68 (dd, 1H), 3.52 (dd, 1H), 2.35 (m, 2H).



27-6

Methyl 4-(2-Pyrrolidinylethyloxy)benzoate (27-6)

Compound 23-2 (2 g, 11.8 mmol) and chloroethylpyrrolidine•HCl (Aldrich) (1.8 g, 11.8 mmol) were treated with NaH (0.94 g, 23.6 mmol) in DMF (30 mL) as described for 27-1 to give 27-6 as a clear oil. R_f (10% MeOH/CHCl₃ saturated with NH₃) 0.4. ¹H NMR (300 MHz, CD₃OD) δ 7.95 (d, 2H), 7.0 (d, 2H), 4.18 (t, 2H), 3.85 (s, 3H), 2.92 (t, 2H), 2.65 (m, 4H), 1.8 (m, 4H).



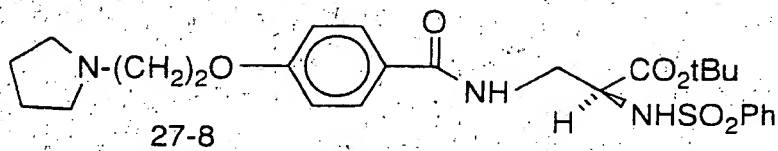
27-7

4-[2-(Pyrrolidinyl)ethyloxy]benzoic acid (27-7)

Compound 27-6 (1.5 g, 6.0 mmol) was treated with 6N HCl for 48 hours at room temperature and 60°C for 2 hours. The solvent was removed to give 27-7 as a white solid.

¹H NMR (400 MHz, D₂O) δ 7.86 (d, 2H), 6.94 (d, 2H), 4.3 (m, 2H), 3.55 (m, 4H), 3.05 (m, 2H), 2.02 (m, 2H), 1.9 (m, 2H).

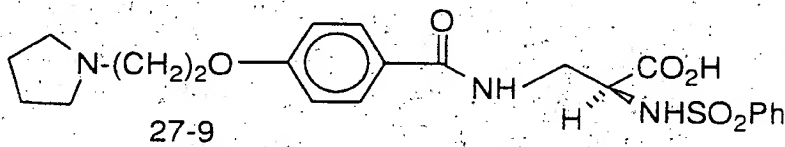
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t-Butyl 4-[2-(Pyrrolidinyl)ethyloxy]benzoyl-2(S)-phenylsulfonylamino- β -alanine t-butyl ester (27-8)

10 27-7 (1.0 g, 3.0 mmol) and 9-12 (0.7 g, 3 mmol) were treated with BOP reagent (1.3 g, 3 mmol) and N-methylmorpholine (10 mL, 9.0 mmol) in CH_3CN (15 mL) as described for 27-3 to give 27-8. R_f (50% EtOAc/ CHCl_3 saturated with NH_3) 0.29.

15 ^1H NMR (400 MHz, DMSO) δ 7.75 (m, 4H), 7.5 (m, 3H), 6.98 (d, 2H), 4.08 (t, 2H), 4.01 (dd, 1H), 3.52 (t, 2H), 3.42 (m, 1H), 3.38 (m, 1H), 2.78 (t, 2H), 2.5 (m, 4H), 2.05 (m, 4H), 1.2 (s, 9H).

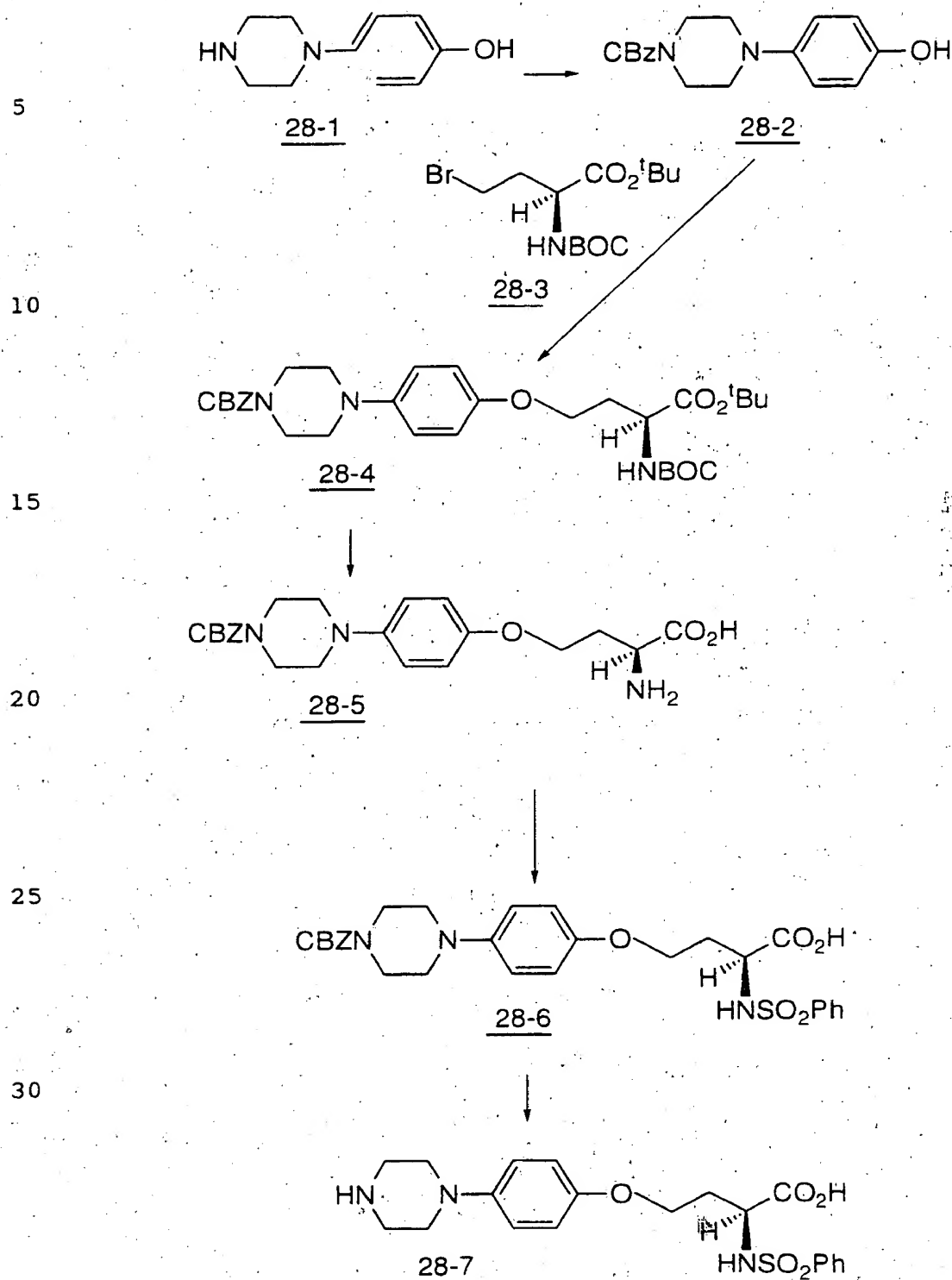


4-[2-(Pyrrolidinyl)ethyloxy]benzoyl-2(S)-phenylsulfonylamino- β -alanine (27-9)

25 A solution of 27-8 (1.0 g, 2.0 mmol) was dissolved in EtOAc (7 mL) and treated with HCl gas as described for 27-5. The crude product was purified by preparative HPLC to give 27-9 as the TFA salt. R_f (10:0.5:0.5 EtOH/ NH_4OH / H_2O) 0.20.

30 ^1H NMR (400 MHz, D_2O) δ 7.62 (d, 2H), 7.44 (d, 2H), 7.3 (m, 3H), 6.9 (d, 2H), 4.28 (m, 2H), 4.06 (m, 1H), 3.65-3.55 (m, 5H), 3.3 (m, 1H), 3.08 (m, 2H), 2.05 (m, 2H), 1.9 (m, 2H).

SCHEME 28



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(N-Benzoyloxycarbonyl-4-piperazinyl)phenol 28-2

4-Piperazinyl phenol (Schweizerhall, 5 g, 30.5 mmol) was dissolved in THF (150 mL), treated with diisopropylethylamine (12.2 mL, 70.0 mmol), and cooled to 0°C. Benzylchloroformate (4.4 mL, 30.5 mmol) was added and the reaction was allowed to warm to room temperature and stir overnight. The solution was diluted with EtOAc, washed with water and brine, dried over MgSO₄, filtered and evaporated to give a brown oil. Column chromatography (SiO₂, 40% EtOAc/hexanes) gave 28-2 as a white solid. R_f (40% EtOAc/hexanes) 0.34.

¹H NMR (400 MHz, CDCl₃) δ 7.4-7.3 (m, 5H), 6.8 (d, 2H), 7.75 (d, 2H), 5.1 (s, 2H), 3.65 (m, 4H), 3.0 (m, 4H).

t-Butyl 2-(S)(t-Butoxycarbonylamino)-4-[4-(N-benzyloxycarbonyl-piperazinyl)phenoxy]butanoate (28-4)

A solution of NaH (2.5 g, 60% dispersion in mineral oil, 1.5 mmol) in DMF (5 mL) was treated with 28-2, (220 mg, 0.7 mmol) and stirred for 10 minutes. A solution of 28-3 (JACS, 1990, 112, 760) (0.2 g, 0.59 mmol) in DMF (2 mL) is added dropwise over 5 minutes. The dark red solution was stirred for 1 hour, then diluted with EtOAc, washed with 10% KHSO₄ and brine, dried over MgSO₄, filtered and evaporated to yield a tan oil. Column chromatography (SiO₂, 30% EtOAc/hexanes) gave 28-4 as a colorless oil. R_f (30% EtOAc/hexanes) 0.3.

¹H NMR (400 MHz, CDCl₃) δ 7.4-7.3 (m, 5H), 6.86 (d, 2H), 6.81 (d, 2H), 5.22 (bs, 1H), 5.15 (s, 2H), 4.34 (m, 1H), 3.95 (m, 2H), 3.64 (m, 4H), 3.0 (m, 4H), 2.26 (m, 1H), 2.14 (m, 1H), 1.46 (s, 9H), 1.43 (s, 9H).

2-(S)-Amino-4-[4-(N-benzyloxycarbonyl piperazinyl)phenoxy]butanoic acid (28-5)

A solution of 28-4 (1.0 g, 1.8 mmol) in 10 mL EtOAc was cooled to -40°C and saturated with HCl gas. The solution was warmed

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to 0°C, then concentrated to give 28-5 as a tan solid. R_f (10:1:1 EtOH/H₂O/NH₄OH) 0.18.

¹H NMR (400 MHz, CD₃OD) δ 7.6 (d, 2H), 7.4-7.3 (m, 5H), 7.13 (d, 2H), 5.15 (s, 2H), 4.2 (m, 2H), 3.95 (bs, 4H), 3.6 (m, 4H), 2.4 (m, 2H).

5
2(S)-(Benzenesulfonylamino)-4-[4-(N-benzyloxycarbonyl piperazinyl)-phenoxy]butanoic acid (28-6)

A solution of 28-5 (0.97 g, 2.2 mmol) in H₂O (26 mL) was cooled to 0°C and treated with 1N NaOH (2.6 mL) and dioxane (13 mL). The solution was treated simultaneously with benzenesulfonyl chloride (0.56 mL in 1.5 mL dioxane, 4.4 mmol) and 1N NaOH so that the pH of the solution remained >10. The reaction was stirred for 1 hour at 0°C, then treated in a similar manner with another portion of benzene sulfonyl chloride, and stirred for 1 hour. The solution was diluted with 10% KHSO₄ and washed with EtOAc. The organic layers were dried (brine, MgSO₄), filtered and evaporated to give a tan oil. Column chromatography (9:0.5:0.5 CH₂Cl₂/MeOH/HOAc) gave 28-6 as a white solid. R_f (9:0.5:0.5 CH₂Cl₂/MeOH/HOAc) 0.26.

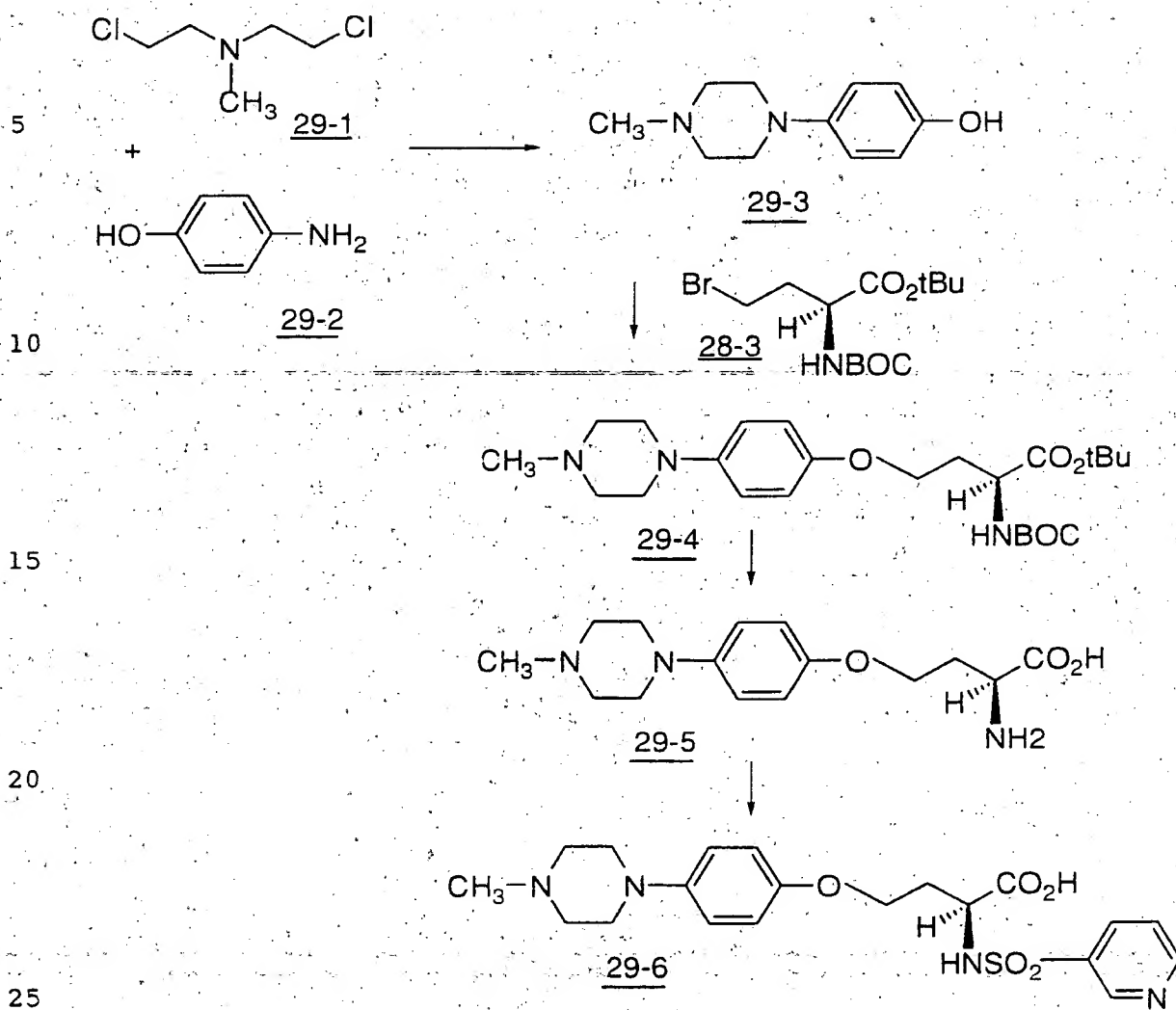
¹H NMR (400 MHz, CD₃OD) δ 7.8 (d, 2H), 7.42-7.25 (m, 8H), 6.9 (d, 2H), 6.7 (d, 2H), 5.12 (s, 2H), 4.03 (dd, 1H), 3.85 (m, 2H), 3.67 (bs, 4H), 3.0 (4H), 2.18 (m, 1H), 1.95 (m, 1H).

2(S)-Phenylsulfonylamino-4-(4-piperazinylphenoxy)butanoic acid (28-7)

Compound 28-6 (0.4 g, 0.7 mmol) was treated with 29% HBr/HOAc for 25 minutes, then concentrated to give a yellow oil. Column chromatography (10:0.5:0.5 EtOH/NH₄OH/H₂O) gave pure 28-7. R_f (10:0.5:0.5 EtOH/H₂O/NH₄OH) 0.17.

¹H NMR (400 MHz, D₂O) δ 7.66 (d, 2H), 7.23 (m, 3H), 7.19 (d, 2H), 6.74 (d, 2H), 4.02 (m, 1H), 3.8 (m, 1H), 3.7 (m, 1H), 3.6 (m, 4H), 3.5 (m, 4H), 2.2-1.8 (m, 2H).

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SCHEME 294-(N-methyl piperazinyl)phenol (29-3)

30 In separate dropping funnels, 29-1 (5.8 g, 30 mmol) in 100 mL acetone and 29-2 (3.27 g, 30 mmol) in 100 mL acetone were added over a period of 1.5 hours to a reaction vessel containing 160 mL H₂O and 120 mL acetone at reflux 30 minutes after addition was completed the acetone was removed in vacuo and the aqueous phase was basified with bicarbonate, saturated with NaCl and extracted with EtOAc. The organic layer was evaporated to give a brown-orange solid. Column

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chromatography (SiO₂, 15% CH₃OH/CHCl₃) gave 29-3 as a yellow solid. R_f (20% CH₃OH/CHCl₃) 0.38.

¹H NMR (300 MHz, CDCl₃) δ 6.8 (d, 2H), 6.7 (d, 2H), 3.1 (m, 4H), 2.6 (m, 4H), 2.3 (s, 3H).

t-Butyl 2(S)-t-Butyloxycarbonylamino-4-[4-N-methylpiperazinyl]-phenoxy]butanoate (29-4)

To a suspension of NaH (0.09 g, 3.75 mmol) in DMF (8 mL) was added 29-3 (0.3 g, 1.65 mmol). After 10 minutes of stirring, 28-3 (0.5 g, 1.5 mmol) was added and the reaction was stirred overnight. The solution was diluted with EtOAc, washed with 10% KHSO₄ and brine, dried (MgSO₄) filtered and evaporated. Column chromatography (SiO₂, 5% CH₃OH/EtOAc) gave 29-4 as a white solid. R_f (10% CH₃OH/EtOAc) 0.43.

¹H NMR (400 MHz, CD₃OD) δ 6.94 (d, 2H), 6.85 (d, 2H), 4.22 (dd, 1H), 3.98 (m, 2H), 3.1 (m, 4H), 2.66 (t, 4H), 2.37 (s, 3H), 2.22 (m, 1H), 2.0 (m, 1H), 1.46 (s, 9H), 1.41 (s, 9H).

2(S)-Amino-3-[4-(N-methylpiperazinyl)phenoxy]butanoic acid (29-5)

A solution of 29-4 (0.06 g, 0.12 mmol) in EtOAc (3 mL) was cooled to -40°C and saturated with HCl gas. The solution was warmed to 0°C, then concentrated to yield 29-5 as an off-white solid. R_f (10:0.1:0.1) EtOH/NH₄OH/H₂O) 0.42.

¹H NMR (300 MHz, CDCl₃) δ 6.99 (d, 2H), 6.85 (d, 2H), 4.1 (m, 3H), 3.55 (m, 4H), 3.0 (m, 2H), 2.9 (s, 3H), 2.3 (m, 2H).

2(S)-3-Pyridylsulfonylamino-4-[4-(N-methylpiperazinyl)-phenoxy]butanoic acid (29-6)

A solution of 29-5 (0.05 g, 0.15 mmol) in H₂O (4 mL) was cooled to 0°C and treated with 1N NaOH (0.3 mL) and dioxane (2 mL). 3-pyridylsulfonyl chloride (JOC, 1989, 54, 389) (0.03 g, 0.15 mmol) was added, along with enough 1N NaOH to keep the pH of the reaction greater than 10. The reaction was concentrated and chromatographed

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(SiO₂, 10:0.1:0.1 EtOH/H₂O/NH₄OH) to give 29-6 as an off-white solid. R_f (10:0.1:0.1) EtOH/H₂O/NH₄OH) 0.79.

¹H NMR (400 MHz, CD₃OD) δ 8.8 (s, 1H), 8.5 (d, 1H), 8.1 (d, 1H), 7.28 (m, 1H), 6.85 (d, 2H), 6.7 (d, 2H), 3.85-3.8 (m, 3H), 2.8 (s, 3H), 2.18 (m, 1H), 1.85 (m, 1H).

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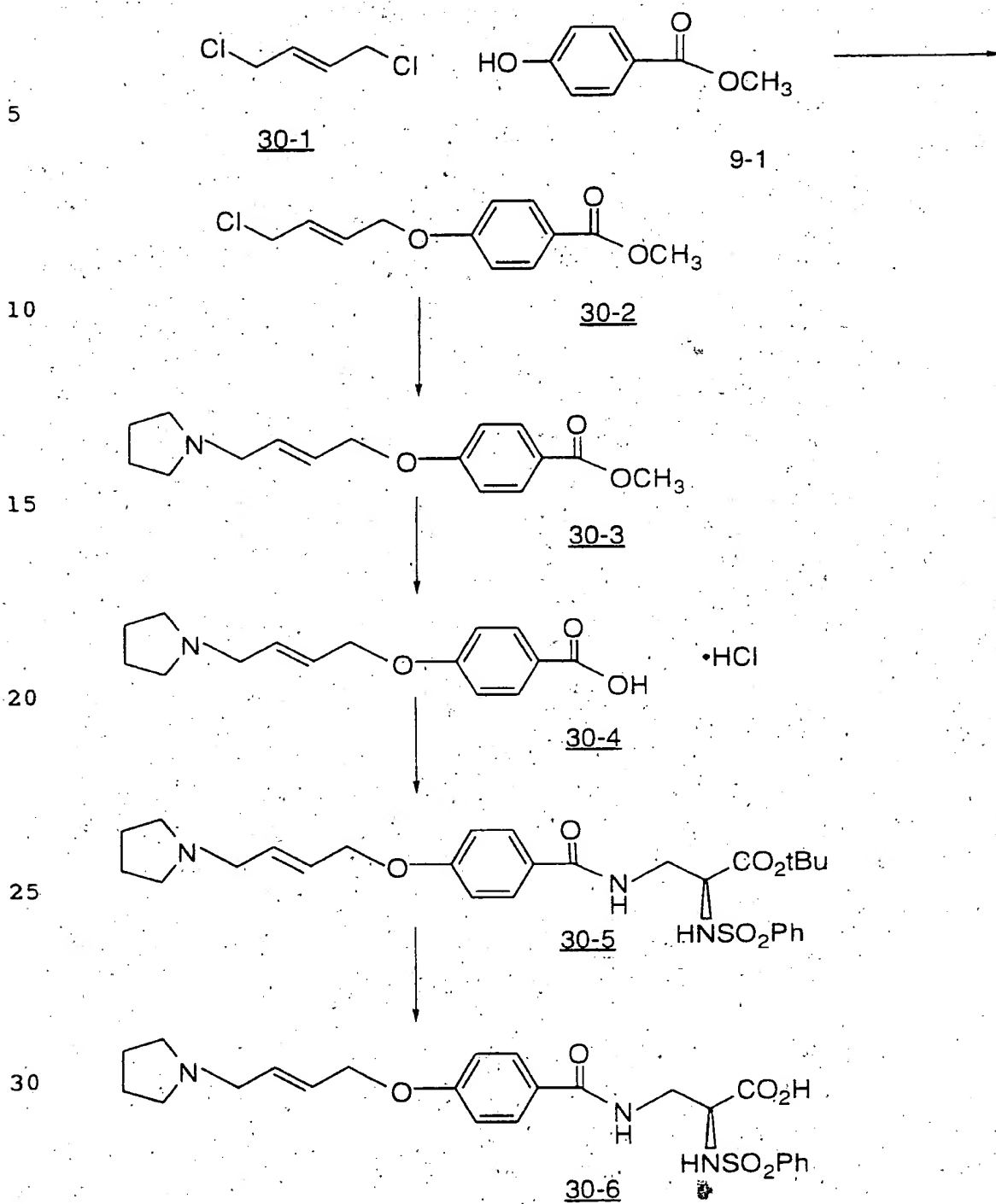
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SCHEME 30

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Methyl 4(4-chlorobut-2-enyloxy)benzoate (30-2)

A solution of 9-1 (1.2g, 8 mmol) and 1,4 dichloro 2-butene (1.6 mL, 17 mmol) (30-1) (Aldrich) in DMF (30 mL) was treated with Cs₂CO₃ (3.9g, 12 mmol) for 24 h. The solvent was removed in vacuo and the residue chromatographed (10% EtOAc/Hexanes) to give 30-2 as a white solid. R_f (20% acetone/hexane) 0.42.

¹H NMR (300 MHz, CDCl₃) δ 8.1 (d, 2H), 7.0 (d, 2H), 6.1 (s, 2H), 4.7 (s, 2H), 4.2 (m, 2H), 3.98 (s, 3H).

Methyl 4-[(4-Pyrrolidinyl-but-2-enyl)oxy]benzoate (30-3)

A solution of 30-2 (1.3 g, 5.36 mmol) in DMF (15 mL) was treated with pyrrolidine (2.4 mL, 29 mmol) and heated at 80°C for 78 h. The solvent was removed in vacuo and the residue was absorbed onto SiO₂ and chromatographed (SiO₂, 0-7% CH₃OH in CH₂Cl₂) to give 30-3 as a yellow oil. R_f (10% CH₃OH/CH₂Cl₂) 0.24.

¹H NMR (300 MHz, CDCl₃) δ 8.0 (d, 2H), 6.9 (d, 2H), 6.0 (m, 2H), 4.6 (d, 2H), 3.85 (s, 3H), 3.28 (d, 2H), 2.7 (m, 4H), 1.85 (m, 4H).

4-[(4-Pyrrolidinylbut-2-enyl)oxy]benzoic acid (30-4)

A solution of 30-3 (1.14 g, 4.14 mmol) in 6 N HCl (30 mL) was heated at 60°C for 24 h. The solution was concentrated and the residue was chromatographed (SiO₂, 9:1:1 EtOH/H₂O/NH₄OH) to give a dark yellow oil. The HCl salt was prepared by dissolving the oil in CH₂Cl₂ and adding 1 M HCl/Et₂O. The solvents were removed and the residue washed with Et₂O to give 30-4 as an off-white solid. R_f (9:1:1 EtOH/H₂O/NH₄OH) 0.2.

4-[(4-Pyrrolidinylbut-2-enyl)oxy]benzoyl-2(S)-phenylsulfonylamino-β-alanine t-butyl ester (30-5)

A suspension of 30-4 (0.77 g, 2.6 mmol) in DMF (7 mL) was treated with N-methyl morpholine (1.5 mL, 14 mmol), CDI (0.5 g, 3.1 mmol) and 19-2a (1.0 g, 3.2 mmol). Concentration and chromatography (SiO₂, 5% CH₃OH/CH₂Cl₂), followed by separation by

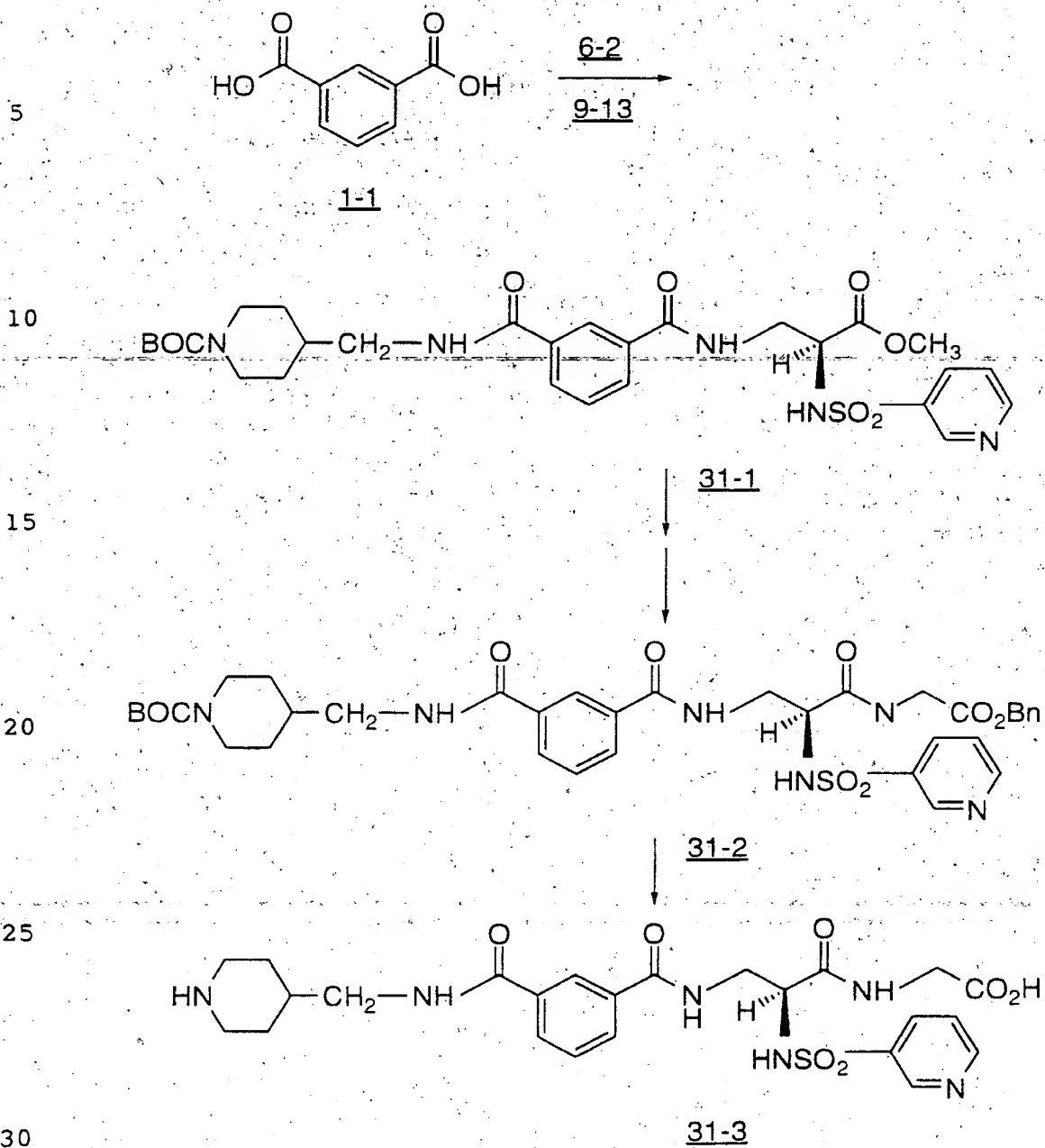
preparative HPLC (reverse phase) gave 30-5 as the TFA salt. R_f (10% CH₃OH/CH₂Cl₂) 0.19.

5 4-[(4-Pyrrolidinyl)but-2-enyl]benzoyl-2(S)-phenylsulfonylamino-β-alanine (30-6)

The compound 30-5 (0.22 g, 0.43 mmol) was treated with 6N HCl (20 mL) for 24 h at room temperature and 1.5 h at 60°C. Concentration of the solution and chromatography of the residue (SiO₂, 9:1:1 EtOH, H₂O, NH₄OH) gave 30-6 as a white solid. R_f (9:1:1 EtOH/H₂O/NH₄OH) 0.69.

10 ¹H NMR (300 MHz, D₂O) δ 7.72 (d, 2H), 7.55 (d, 2H), 7.5 (m, 3H), 7.0 (d, 2H), 6.2 (m, 1H), 5.9 (m, 1H), 3.85 (dd, 1H), 3.8 (d, 2H), 3.6 (m, 3H), 3.45 (m, 2H), 3.38 (dd, 1H), 3.0 (m, 2H), 2.0 (m, 4H).

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SCHEME 31

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3-[(N-Boc-Piperidin-4-ylmethyl)aminocarbonyl]benzoyl-2(S)-3-pyridylsulfonylamino- β -alanine methyl ester (31-1)

Treatment of 1-1 with CDI, 6-2 and 9-13 as described for 1-2 gave 31-1 after column chromatography (60% acetone/hexanes).

¹H NMR (300 MHz, CDCl₃) δ 9.0 (s, 1H), 8.64 (d, 1H), 8.14 (s, 1H), 8.07 (d, 1H), 7.9 (d, 1H), 7.8 (d, 2H), 7.4-7.3 (m, 3H), 4.33 (m, 1H), 4.1-4.0 (bd, 2H), 3.9-3.65 (m, 2H), 3.57 (s, 3H), 3.2 (bs, 2H), 2.6 (m, 2H), 1.8-1.6 (m, 3H), 1.43 (s, 9H), 1.2-1.0 (m, 2H).

3-[(N-Boc-Piperidin-4-ylmethyl)aminocarbonyl]benzoyl-2(S)-3-pyridylsulfonylamino- β -alanyl-glycine benzyl ester (31-2)

A solution of 31-1 (0.75 g, 1.5 mmol) in 1:1:1 THF/MeOH/H₂O (15 mL) was treated with LiOH·H₂O (0.37 g, 8.8 mmol). After 45 min. the solution was concentrated, diluted with water, washed with EtOAc. The aqueous layer was acidified to pH 2-3 with 10% KHSO₄ and extracted with EtOAc. The organic layer was dried (Na₂SO₄), filtered and evaporated to give an acid which was dissolved in acetonitrile (3 mL) and treated with glycine benzyl ester·HCl (0.1 g, 0.5 mmol), N-methylmorpholine (0.11 mL, 0.98 mmol), and BOP reagent (0.26 g, 0.58 mmol) for 24 h. The solution was concentrated, dissolved in water and EtOAc and the layers separated. The organic layer was dried (Na₂SO₄), filtered and evaporated. Column chromatography (SiO₂, 70% acetone/hexanes) gave 31-2 as a white solid.

¹H NMR (300 MHz, CDCl₃ + CD₃OD) δ 8.98 (s, 1H), 8.43 (d, 1H), 8.1 (d, 1H), 7.95 (m, 2H), 7.78 (d, 1H), 7.4-7.3 (m, 5H), 7.2 (m, 2H), 5.1 (s, 2H), 4.18 (dd, 1H), 4.05 (m, 2H), 3.7 (dd, 1H), 3.55 (dd, 1H), 3.3 (m, 2H), 1.8-1.7 (m, 3H), 1.43 (s, 9H), 1.15 (m, 2H).

3-[(Piperidin-4-ylmethyl)aminocarbonyl]benzoyl-2(S)-3-pyridylsulfonylamino- β -alanyl-glycine (31-3)

Compound 31-2 (0.12 g) was treated with 6N HCl for 24 h. The solution was concentrated and chromatographed (SiO₂, 9:1:1 EtOH/H₂O/NH₄OH) to give 31-3 as a white solid.

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^1H NMR (300 MHz, D_2O) δ 8.84 (s, 1H), 8.3 (m, 1H), 8.19 (d, 1H), 7.9 (m, 2H), 7.7 (d, 1H), 7.58 (t, 1H), 7.35 (m, 1H), 4.28 (dd, 1H), 3.78 (s, 2H), 3.5-3.35 (m, 6H), 3.0 (t, 2H), 2.0 (m, 3H), 1.5 (m, 2H).

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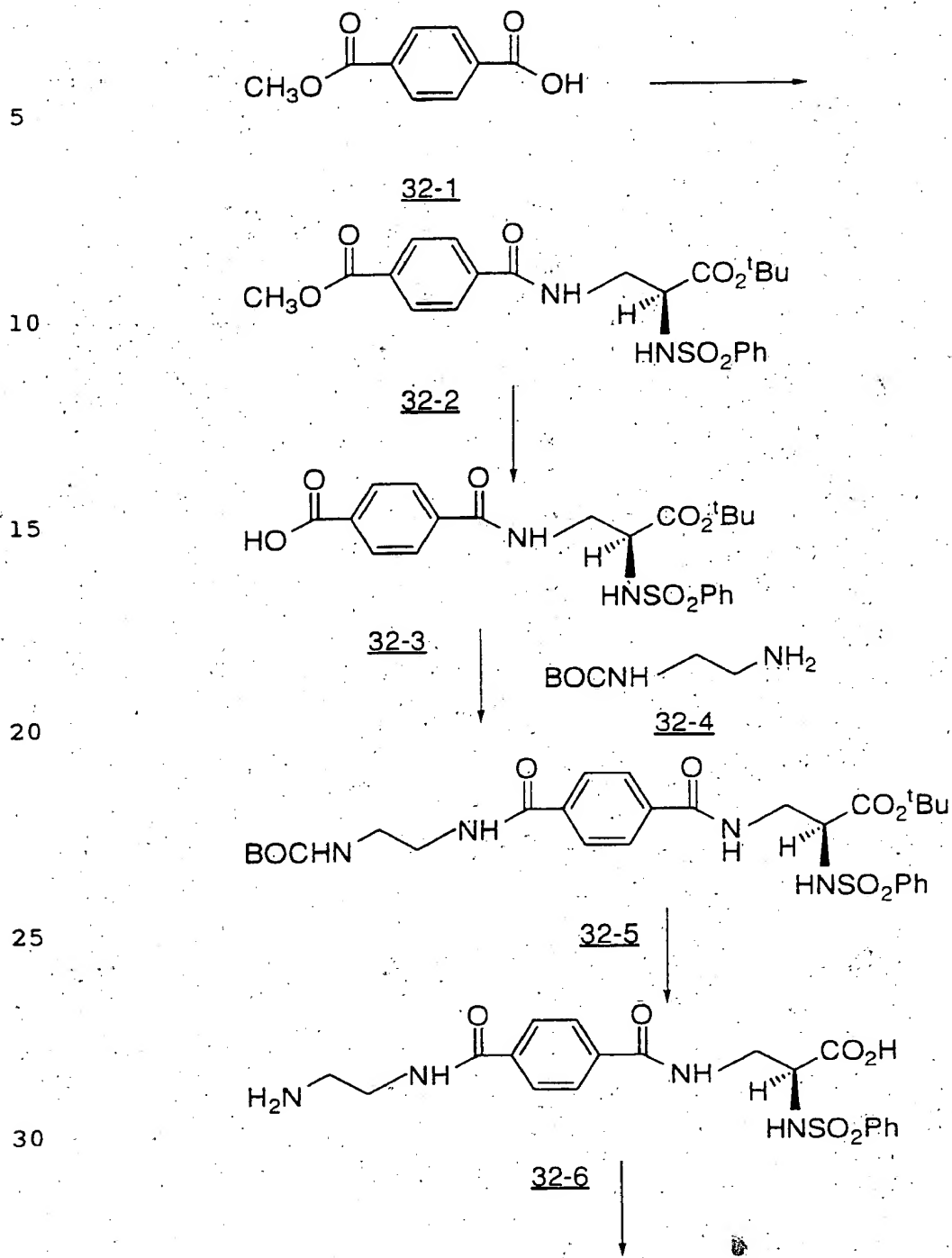
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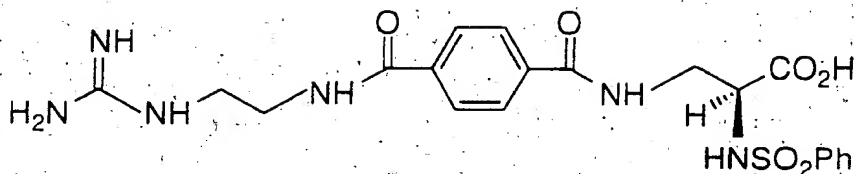
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SCHEME 32

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32-7

4-(Methyloxycarbonyl)benzoyl-2(S)-phenylsulfonylamino- β -alanine t-butyl ester (32-2)

A slurry of mono-methyl terephthalic acid (32-1, Aldrich) (0.25 g, 1.4 mmol) and 19-2a (0.5 g, 1.4 mmol) in acetonitrile (7 mL) was treated with N-methyl morpholine (0.31 mL, 2.8 mmol) and BOP reagent (0.62 g, 1.4 mmol) for 24 h. The solution was diluted with EtOAc, washed with H₂O, 10% KHSO₄, saturated NaHCO₃ and brine. The organic layer was dried over MgSO₄, filtered and evaporated to give a tan solid. Column chromatography (40% EtOAc/Hexanes) gave 32-2 as a white solid.

¹H NMR (400 MHz, CDCl₃) δ 8.1 (d, 2H), 7.8 (m, 4H), 7.59 (m, 1H), 7.50 (m, 2H), 6.8 (m, 1H), 5.6 (d, 1H), 3.98-3.9 (m, 2H), 3.95 (s, 3H), 3.55 (m, 1H), 1.29 (s, 9H).

4-(Carboxyl)benzoyl-2(S)-phenylsulfonylamino- β -alanine t-butyl ester (32-3)

A solution of 32-2 (0.58 g, 1.25 mmol) in 1:1:1 THF/MeOH/H₂O is treated with LiOH (0.1, 1.25 mmol) for 2 h. The reaction was diluted with 10% KHSO₄ and extracted with EtOAc. The organic layer was washed with H₂O, brine, dried over MgSO₄, filtered and evaporated to give 32-3 as a white solid.

¹H NMR (CD₃OD, 400 MHz) δ 8.09 (d, 2H), 7.85 (m, 3H), 7.5 (m, 4H), 4.13 (dd, 1H), 3.7 (m, 1H), 3.52 (m, 1H), 1.23 (s, 9H).

(1-t-Butoxycarbonylamino-2-amino)ethane (32-4)

A solution of ethylenediamine (Aldrich) 18 g, 0.3 mol) in CHCl₃ (300 mL) was treated dropwise with a solution of BOC anhydride (13.1 g, 0.06 mole) in CHCl₃ (100 mL) over 1 h, then stirred

- 185 -

overnight. The reaction was filtered and the filtrate concentrated to give 32-4 as a viscous, colorless oil.

¹H NMR (300 MHz, CDCl₃) δ 4.9 (bs, 1H), 3.15 (m, 2H), 2.28 (m, 2H), 1.43 (s, 9H), 1.1 (bs, 2H).

5 4-[2-(N-Boc-Amino)ethylaminocarbonyl]benzoyl-2(S)-phenylsulfonyl-amino-β-alanine t-butyl ester (32-5)

A solution of 32-3 (0.5 g, 1.1 mmol) and 32-4 (0.26 g, 1.67 mmol) in acetonitrile (8 mL) is treated with N-methylmorpholine (0.18 mL, 1.67 mmol) and BOP reagent (0.74 g, 1.67 mmol) for 24 h. The solution is diluted with EtOAc, washed with H₂O, 10% KHSO₄, sat. NaHCO₃, brine, dried over MgSO₄, filtered and evaporated. Column chromatography (80% EtOAc/Hexanes) gave 32-5 as a white solid. R_f (80% EtOAc/Hexanes) 0.22.

15 ¹H NMR (400 MHz, CDCl₃) δ 7.7-7.6 (m, 6H), 7.5 (m, 1H), 7.55 (m, 1H), 7.45 (m, 2H), 7.35 (m, 1H), 5.2 (m, 1H), 4.0 (dd, 1H), 3.8 (m, 1H), 3.67 (m, 1H), 3.52 (m, 2H), 3.4-3.3 (m, 2H), 1.42 (s, 9H), 1.27 (s, 9H).

20 4-[(2-Aminoethyl)aminocarbonyl]benzoyl-2(S)-phenylsulfonylamino-β-alanine (32-6)

A slurry of 32-5 (0.62 g, 1.05 mmol) in EtOAc (15 mL) was cooled to -40°C and saturated with HCl gas. The reaction was warmed to 0°C, then concentrated to yield 32-6 as a white solid.

25 ¹H NMR (400 MHz, CD₃OD) δ 7.9-7.6 (m, 6H), 7.6-7.4 (m, 4H), 4.21 (dd, 1H), 3.75 (dd, 1H), 3.67 (m, 2H), 3.5 (m, 1H), 3.2 (m, 2H).

4-[(2-Guanidinoethyl)aminocarbonyl]benzoyl-2(S)-phenylsulfonyl-amino-β-alanine (32-7)

30 A solution of 32-6 (0.56 g, 1.2 mmol) in 1:1 DMF/H₂O (8 mL) was treated with diisopropylethylamine (0.63 mL, 3.6 mmol) and N-amidinoimidazole (Fluka, (0.26 g, 1.8 mmol)) and heated to 40°C for 4.5 h. Column chromatography (10:0.2:0.2 EtOH/H₂O/NH₄OH,

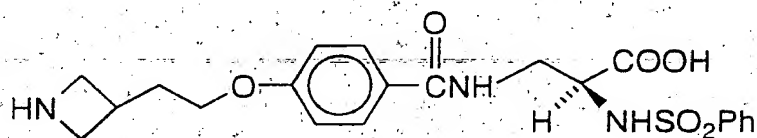
- 186 -

followed by 10:1:1 EtOH/H₂O/NH₄OH) gave 32-7. R_f (10:1:1 EtOH/H₂O/NH₄OH) 0.10.

¹H NMR (400 MHz, DMSO) δ 8.8 (m, 2H), 8.4 (s, 1H), 7.91 (d, 2H), 7.78 (d, 2H), 7.75 (d, 2H), 7.5 (m, 7H), 7.0 (bs, 1H), 3.45-3.2 (m, 7H).

SCHEME 33

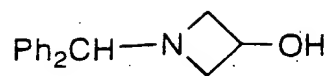
In order to prepare [3-(Azetidinyl)ethyloxy]phenyl-carbonyl-2(S)-phenylsulfonylamino-β-alanine,



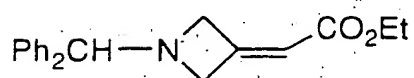
33-7

a procedure similar to the procedure followed in Scheme 9 was used, substituting 1-4 with N-BOC-Azetidin-3-ylethyl iodide (33-6).

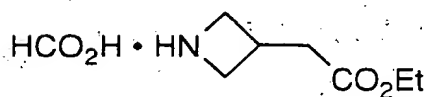
- 187 -

33-1

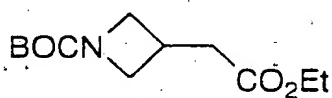
a) CH2Cl2, oxalyl chloride,
DMSO, NEt3
b) Ph3P=CHCO2Et

33-2

10% Pd/C, HCO2H, CH3OH

33-3

BOC2O, DMF, NEt3

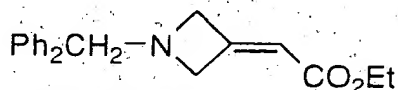
33-4

LiBH4, Et2O

33-5

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↓ I₂, PPh₃, imidazole, CH₃CN

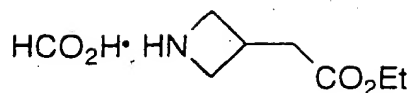
33-633-2

15 N-Diphenylmethyl-3-(carboethoxymethylidene)-3-azetidine (33-2)

To a solution of oxalyl chloride (0.10 mL, 1.1 mmol), in CH₂Cl₂ (4.7 mL) at -78°C was added DMSO (0.12 mL, 1.7 mmol) dropwise. After gas evolution subsided (~5 min), a solution of 33-1 (for preparation see; JOC, 37, 3953, 1972 A.G. Anderson, R. Lok) (0.20 g, 0.84 mmol) in CH₂Cl₂ (1.5 mL) was added. After 30 min., NEt₃ (0.40 mL, 2.8 mmol) was added and after 10 min. the cooling bath removed. After 20 min. TLC analysis indicated no starting material remained. The ylide (0.32 g, 0.92 mmol) was then added and the reaction stirred for 20 h. The reaction mixture was diluted with pet. ether and then washed with H₂O, 5% KHSO₄, and brine, dried (MgSO₄), and concentrated. Flash chromatography (silica, (15% EtOAc/hex) gave 33-2 (0.14 g) as a colorless oil. R_f 0.43 (silica, 15% EtOAc/hexanes).

1H NMR (300 MHz, CDCl₃) δ 7.50-7.10 (m, 10H), 5.65 (m, 1H), 4.52 (s, 1H), 4.16 (m, 2H), 4.14 (q, J = 7 Hz, 2H), 3.89 (m, 2H), 1.22 (t, J = 7 Hz, 3H).

30

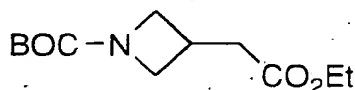


33-3

Ethyl Azetidin-3-ylacetate•formate (33-3)

A mixture of 33-2 (3.2 g, 10.3 mmol), 4.4% HCO₂H/CH₃OH (317 mL), and 10% Pd/C (0.63 g) was stirred under a hydrogen atmosphere (1 atm) at ambient temperature. After stirring over the weekend the reaction mixture was filtered through a celite pad and the filtrate concentrated to give 33-3 as a colorless oil as used directly for the next reaction.

¹H NMR (300 MHz, CDCl₃) δ 9.90 (bs, 2H), 8.37 (s, 2H), 4.19 (m, 2H), 4.17 (q, J = 7 Hz, 2H), 3.89 (m, 2H), 3.26 (m, 1H), 2.72 (d, J = 8 Hz, 2H), 1.26 (t, J = 7 Hz, 3H).



33-4

Ethyl N-BOC-azetidin-3-ylacetate (33-4)

A stirred solution of 33-3 (10.3 mmol), DMF (50 mL), and NEt₃ (5.0 mL, 36.0 mmol) at 0°C was treated with BOC₂O (2.5 g, 11.3 mmol) followed by removal of the cooling bath. After 20 h, the reaction mixture was diluted with EtOAc and then washed with H₂O, 5% KHSO₄, sat. NaHCO₃, and brine, dried (MgSO₄), and concentrated. Flash chromatography (silica, 30% EtOAc/hexanes) gave 33-4 (1.0 g) as a colorless oil. R_f 0.44 (silica, 30% EtOAc/hexanes).

¹H NMR (300 MHz, CDCl₃) δ 4.13 (q, J = 7 Hz, 2H), 4.01 (m, 2H), 3.60 (dd, J = 9, 6 Hz, 1H), 2.88 (m, 1H), 2.61 (d, J = 8 Hz, 2H), 1.44 (s, 9H) 1.25 (t, J = 7 Hz, 3H).

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33-5N-BOC-Azetidin-3-ylethanol (33-5)

A stirred solution of 33-4 (0.96 g, 3.9 mmol) in ether (20 mL) at ambient temperature was treated with LiBH₄ (0.34 g, 15.8 mmol) then heated to 55°C. After 45 min the cooled reaction was quenched with 5% KHSO₄ (10 mL) and then diluted with EtOAc. The organic phase was washed with 5% KHSO₄ and brine, dried (MgSO₄), and concentrated to give 33-5 (0.79 g) as a colorless oil. R_f 0.46 (silica, EtOAc).

¹H NMR (300 MHz, CDCl₃) δ 4.04 (m, 2H), 3.70-3.50 (m, 4H), 2.63 (m, 1H), 1.83 (m, 2H), 1.44 (s, 9H).

33-6N-BOC-Azetidin-3-ylethyl iodide (33-6)

A stirred solution of 33-5 (0.78 g, 3.8 mmol), PPh₃ (1.1 g, 4.3 mmol), imidazole (0.40 g, 5.8 mmol), and CH₃CN (20 mL) at 0°C was treated with iodine (1.0 g, 4.3 mmol). After 15 min the cooling bath was removed and stirring continued for 5 h. The reaction mixture was then diluted with H₂O and extracted with hexanes (5x25 mL then 4x50 mL). The combined extracts were dried (MgSO₄) and concentrated. Flash chromatography (silica, 20% EtOAc/hexanes) gave 33-6 (0.99 g) as a colorless oil. R_f 0.44 (silica, 20% EtOAc/hexanes).

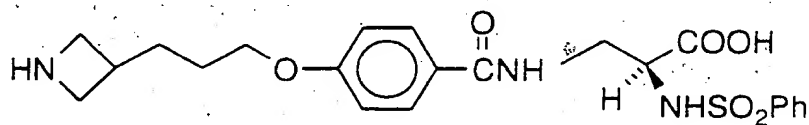
¹H NMR (400 MHz, CDCl₃) δ 4.04 (t, J = 7 Hz, 2H), 3.57 (dd, 2H), 3.10 (t, 2H), 2.64 (m, 1H), 2.16 (q, 2H), 1.43 (s, 9H).

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Substituting 33-6 for 1-4 in Scheme 9, 33-7 is formed.

SCHEME 34

In order to prepare 4-[3-(Azetidin-3-yl)propyloxy]benzoyl-2(S)-phenylsulfonylamino- β -alanine



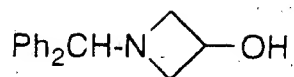
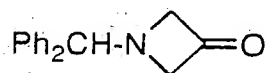
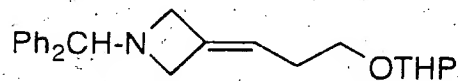
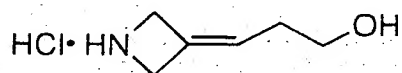
34-7

a procedure similar to the procedure followed in Scheme 33 may be used, substituting 33-5 with 3-(N-BOC-Azetidin-3-yl)propanol (34-6).

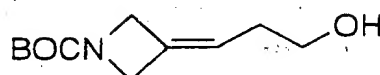
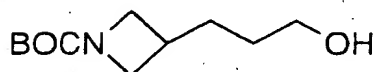
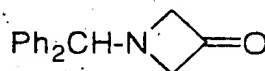
- 192 -

ES01130210T

US93/11623

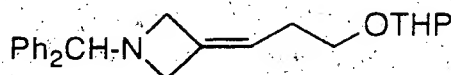
34-1 CH_2Cl_2 , DMSO, oxalyl chloride, Et_3N 34-2THF, -78°C , n-BuLi,
 $\text{Br}^-\text{Ph}_3^+ \text{P}^-(\text{CH}_2)_3\text{O-THP}$ 34-3 $\text{ClCH}_2\text{CH}_2\text{Cl}$, 1-chloroethyl-
chloroformate34-4

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34-4BOC₂O, NEt₃, DMF34-510% Pd/C, H₂, CH₃OH34-634-2N-Diphenylmethyl-azetidin-3-one (34-2)

To a stirred solution of oxalyl chloride (8.7 mL) in CH₂Cl₂ (400 mL) at -78°C, was added DMSO (10.3 mL, 0.13 mol) dropwise. After gas evolution subsided, the alcohol 34-1 (17.5 g, 73 mmol) in CH₂Cl₂ (200 mL) was added. After 15 min, the white suspension was treated dropwise with NEt₃ (51.4 mL, 0.36 mol). After addition was complete, the cooling bath was removed and stirring was continued for 2 h. The reaction mixture was diluted with CH₂Cl₂ and then washed with H₂O and brine, dried (MgSO₄) and 34-2 conc. to a yellow oil. R_f 0.63 (silica, 30% EtOAc/hexanes). ¹H NMR (400 MHz, CDCl₃) δ 7.50-7.20 (m, 10H), 4.59 (s, 1H), 4.00 (s, 4H).

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5

34-3

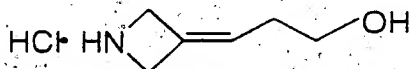
2-[(N-Diphenylmethyl-azetidin-3-yl)methylidene]ethoxy-
tetrahydropyran ether (34-3)

10

A mixture of the phosphonium salt (for preparation see; Schow, S.R., McMorris, T.C., JOC, 44, 3760, 1979) (32.5 g, 66 mmol) in THF (300 mL) at -78°C was treated with *n*-BuLi (44.6 mL, 71 mmol, 1.6 M/hexanes) dropwise then stirred for 1.0 h. The ketone 34-2 (15.4 g, 65 mmol) was then added followed by removal of the cooling bath. After 20 h, the reaction mixture was diluted with EtOAc then washed with H_2O , and brine, dried (MgSO_4), and concentrated. Flash chromatography (silica, 10% EtOAc/hexanes) gave 34-3 (5.8 g) as an oil. R_f 0.50 (silica, 20% EtOAc/hexanes). ^1H NMR (400 MHz, CDCl_3) δ 7.50-7.20 (m, 10H), 5.24 (bs, 1H), 4.56 (m, 1H), 4.48 (bs, 1H), 3.90-3.65 (m, 6H), 3.48 (m, 1H), 3.37 (m, 1H), 2.15 (m, 2H), 1.85-1.45 (m, 6H).

15

20



25

34-4

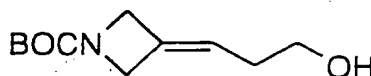
2-[(3-Dehydroazetidin-3-yl)methylene]ethanol (34-4)

30

To a stirred solution of 34-3 (2.4 g, 6.63 mmol) in CH_2Cl_2 (66 mL) at 0°C was added 1-chloroethyl chloroformate (0.73 mL, 6.65 mmol) followed by refluxing for 4.0 h. The reaction mixture was concentrated and the residue dissolved in CH_3OH (66 mL) and refluxed

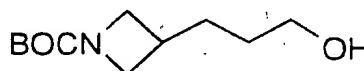
- 195 -

for 1 h. Concentration gave crude 34-4 as an orange oil. R_f 0.18 (silica, 4:1:1 CH₂Cl₂/CH₃OH/AcOH).

34-5

10 2-[(N-BOC-3-Dehydroazetidin-3-yl)methylene]ethanol (34-5)

A solution of 34-4 (2.4 g, 6.63 mmol), DMF (66 mL), and NEt₃ (1.1 mL, 8.0 mmol) at ambient temperature was treated with BOC₂O (1.7 g, 8.0 eq). After 1.0 h, the reaction mixture was diluted with EtOAc and then washed with 10% KHSO₄, H₂O and brine, dried (MgSO₄), and concentrated. Flash chromatography (silica, 60% EtOAc/hexanes) gave 34-5 (560 mg). R_f 0.51 (silica, EtOAc).
 15 ¹H NMR (300 MHz, CDCl₃) δ 5.33 (m, 1H), 4.47 (m, 4H), 3.65 (m, 2H), 2.19 (m, 2H), 1.44 (s, 9H).

34-6

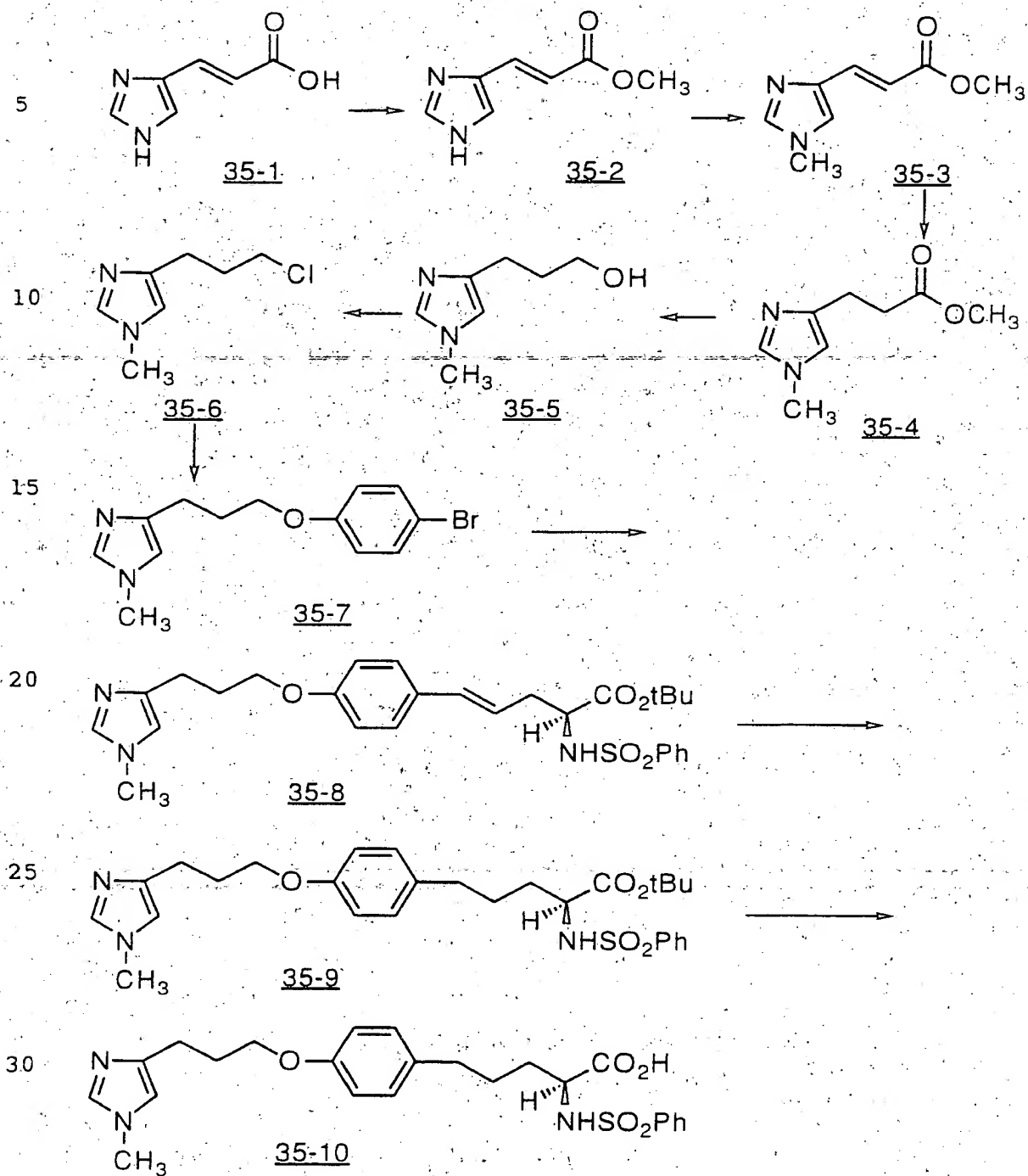
25 3-(N-BOC-Azetidin-3-yl)propanol (34-6)

A mixture of 34-5 (560 mg, 2.62 mmol), CH₃OH (26 mL), and 10% Pd/C (112 mg) was stirred under a hydrogen atmosphere (1 atm) at ambient temperature. After 20 h, the reaction mixture was filtered through a celite pad and the filtrate concentrated to give 34-6 (529 mg) as a yellow oil. R_f 0.38 (silica, EtOAc).
 30 ¹H NMR (400 MHz, CDCl₃) δ 3.99 (t, 2H), 3.64 (t, 2H), 3.53 (dd, 2H), 2.50 (m, 1H), 1.70-1.50 (m, 2H), 1.45 (s, 9H).

Substituting 34-6 for 33-5 in Scheme 33, 34-7 is formed.

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SCHEME 35



Methyl 3-(Imidazol-4-yl)-2-propenoate hydrochloride (35-2)

A slurry of uraconic acid (35-1) (Aldrich) 22.6 g, 16.5 mmol) in CH₃OH (200 mL) was saturated with HCl gas and allowed to stir overnight. The slurry was concentrated to give 35-2 as a white solid.

R_f (5% CH₃OH/EtOAc) 0.676.

¹H NMR (400 MHz, CD₃OD) δ 9.03 (s, 1H), 7.9 (s, 1H), 7.59 (d, 1H), 6.71 (d, 1H), 3.78 (s, 3H).

Methyl 3-(1-Methylimidazol-4-yl)-2-propenoate (35-3)

NaH (0.85g of a 60% dispersion in oil, 21.2 mmol) was placed in a flask, suspended in hexanes, and allowed to settle. The hexanes was decanted and DMF (50 mL) was added, followed by 35-2 (2g, 10.6 mmol). After 10 minutes methyl iodide (0.79 mL, 12.7 mmol) was added. After stirring for 24 hr the solution was diluted with EtOAc and H₂O and the layers were separated. The water layer was basified to pH 11 with saturated NaHCO₃ and extracted with EtOAc and CH₂Cl₂. The organic layers were combined and evaporated. The residue was chromatographed (5% CH₃OH/CHCl₃ saturated with NH₃) to give 35-3 as a white solid.

R_f (50% acetone/hexanes) 0.22

¹H NMR (400 MHz, CD₃OD) δ 7.63 (s, 1H), 7.5 (d, 1H), 7.39 (s, 1H), 6.41 (d, 1H), 3.72 (s, 3H), 3.71 (s, 3H).

Methyl 3-(1-Methylimidazol-4-yl) propanoate (35-4)

A solution of 35-3 (3.8g, 24.7 mmol) in CH₃OH (75 mL) was flushed with argon and 10% Pd/Carbon (0.8 g as a slurry in CH₃OH) was added. The reaction was placed under hydrogen (balloon pressure) and stirred for 24 hr. The slurry was filtered and the filter cake (Solka-Floc) was washed with CH₃OH. The filtrate was concentrated and the residue was dissolved in EtOAc, washed with saturated NaHCO₃, dried (Na₂SO₄) filtered and evaporated. Chromatography (SiO₂, 60% acetone/hexanes) gave 35-4 as a yellow oil.

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R_f (50% acetone/hexanes) 0.19.

¹H NMR (300 MHz, CDCl₃) δ 7.31 (s, 1H), 6.63 (2, 1H), 3.67 (s, 3H), 3.62 (s, 3H), 3.288 (t, 2H), 2.67 (t, 2H).

5 3-(1-Methylimidazol-4-yl)propan-1-ol (35-5)

A solution of 35-4 (1.5 g, 8.9 mmol) in THF (30 mL) was treated with lithium aluminum hydride (1M in THF, 5.5 mL, 55 mmol). After 1.5 hr the reaction is quenched with sodium/potassium tartrate solution and extracted with EtOAc. The aqueous layer was concentrated to dryness and the residue was triturated with EtOAc, then with CH₂Cl₂, then with 10:1 CHCl₃/CH₃OH. The organic extracts were all combined and concentrated to give 35-5.

R_f (10% CH₃OH/CHCl₃) 0.33

15 ¹H NMR (400 MHz, CD₃OD) δ 7.46 (s, 1H), 6.79 (s, 1H), 3.64 (s, 3H), 3.56 (t, 2H), 2.57 (t, 2H), 1.81 (m, 2H).

1-Chloro-3-(1-methylimidazol-4-yl)propane (35-6)

Compound 35-5 (0.8g, 6.45 mmol) was added portion-wise to thionyl chloride (2.5 mL) with stirring. After 4 hr the reaction was concentrated and the residue was chromatographed (SiO₂, 10% CH₃OH/EtOAc) to give 35-6.

R_f (10% CH₃OH/EtOAc) 0.35

25 ¹H NMR (400 MHz, CD₃OD) δ 8.78 (s, 1H), 7.37 (s, 1H), 3.88 (s, 3H), 3.61 (t, 2H), 2.85 (t, 2H), 2.11 (m, 2H).

1-Bromo-4-[3-(1-methylimidazol-4-yl)propyloxy]benzene (35-7)

A solution of 4-hydroxy bromo-benzene (0.25 g, 1.4 mmol) in DMF (5 mL) was treated with NaH (0.056 g, 1.4 mmol, 60% dispersion in oil). After 15 minutes 35-6 (0.05 g, 0.35 mmol) was diluted with H₂O, concentrated, and the residue chromatographed (SiO₂, 10% CH₃OH/EtOAc) to give 35-7.

R_f (10% CH₃OH/EtOAc) 0.25

30 ¹H NMR (400 MHz, CD₃OD) δ 7.45 (s, 1H), 7.33 (d, 2H), 6.8 (m, 3H), 3.92 (t, 2H), 3.62 (s, 3H), 2.67 (t, 2H), 2.03 (m, 2H).

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t-Butyl 2(S)-Phenylsulfonylamino-5-[4-(3-(1-methylimidazol-4-yl)-propyloxy)phenyl]pent-4-enoate (35-8)

5 A solution of 35-7 (0.2g, 0.68 mmol) in CH₃CN (5 mL) was treated with 35-11 (0.25 g, 0.8 mmol), triethylamine (0.19 mL, 1.3 mmol), Pd (OAc)₂ (0.015g, 0.068 mmol) and triorthotolyl phosphine (0.125 g, 0.41 mmol) heated to 110°C for 20 hr. The solution was concentrated and the residue was chromatographed (10% CH₃OH/EtOAc) to give 35-8 as an off-white solid.

10 R_f (10% CH₃OH/EtOAc) 0.24

¹H NMR (400 MHz, CD₃OD) δ 8.72 (s, 1H), 7.81 (d, 2H), 7.55 (m, 1H), 7.49 (t, 2H), 7.32 (s, 1H), 7.21 (d, 2H), 6.8 (d, 2H), 6.42 (d, 1H), 5.92 (m, 1H), 4.02 (t, 2H), 3.86 (s, 3H), 2.88 (t, 2H), 2.5 (m, 2H), 1.2 (s, 9H).

t-Butyl 2(S)-Phenylsulfonylamino-5-[4-(3-(1-methylimidazol-4-yl)-propyloxy)phenyl]pentanoate (35-9)

20 A solution of 35-8 (0.07 g, 0.146 mmol) in CH₃OH (1 mL) was treated with 10% Pd/carbon (0.017g) and placed under hydrogen (balloon). After 20 hr the solution was filtered and concentrated. The residue was purified by preparative HPLC (reverse phase, 95:5 → 50:50 water/acetonitrile) to give 35-9.

R_f (10% CH₃OH/EtOAc) 0.19

25 ¹H NMR (400 MHz, D₂O) δ 8.32 (s, 1H), 7.68 (d, 2H), 7.53 (m, 1H), 7.45 (t, 2H), 6.98 (d, 2H), 6.73 (d, 2H), 3.94 (t, 2H), 3.64 (s, 3H), 3.6 (m, 1H), 2.71 (t, 2H), 2.38 (m, 2H), 1.95 (m, 2H), 1.4 (m, 2H), 1.08 (s, 9H).

2(S)-Phenylsulfonylamino-5-[4-(3-(1-methylimidazol-4-yl)propyloxy)-phenyl]pentanoic acid (35-10)

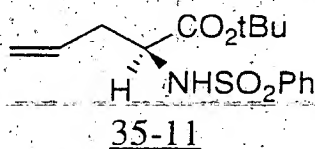
30 A solution of 35-9 (0.055g, 0.127 mmol) in EtOAc (1 mL) was cooled to -78°C, and saturated with HCl gas. The reaction was warmed to 0°C for 1/2 hr, then concentrated and the residue

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chromatographed (20:1:1 EtOH/NH₄OH/H₂O) to give 35-10 as a white solid.

R_f (10:1:1 EtOH/NH₄OH/H₂O) 0.78

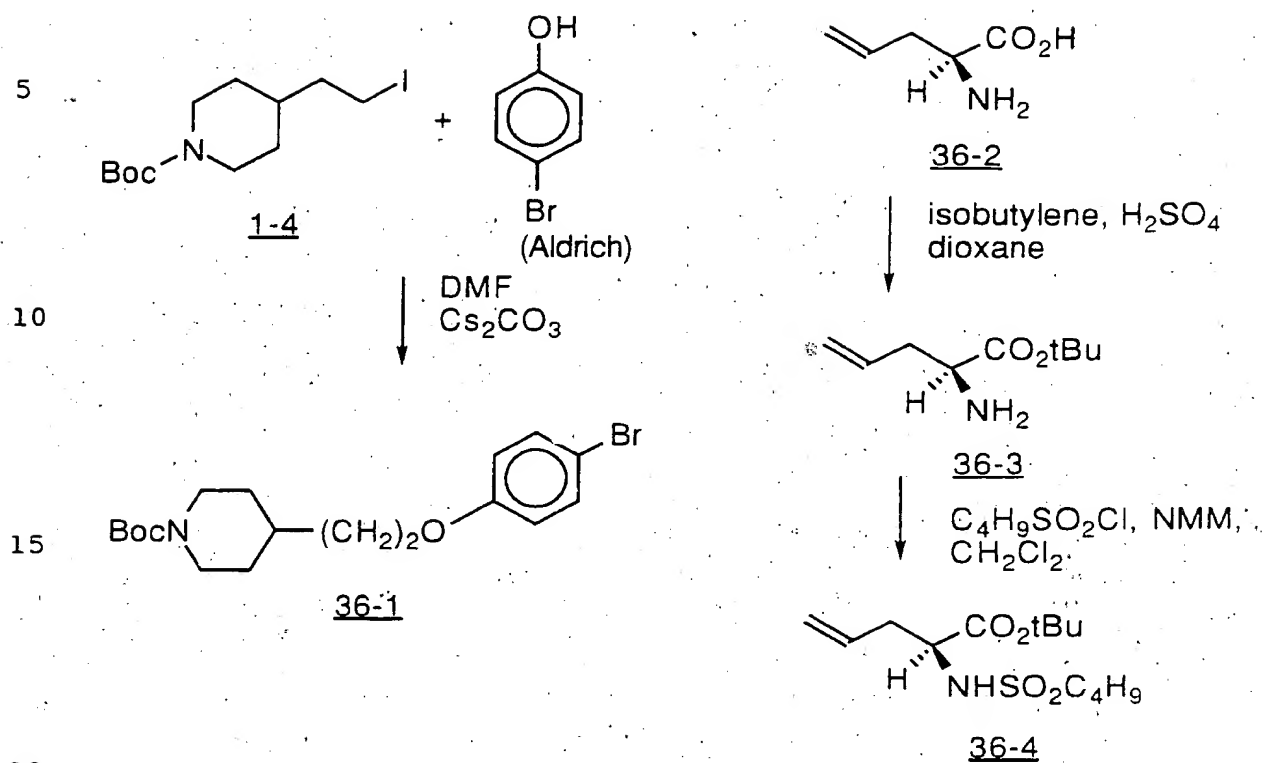
¹H NMR (400 MHz, D₂O) δ 8.23 (s, 1H), 7.71 (d, 2H), 7.52 (m, 1H), 7.44 (t, 2H), 6.96 (m, 3H), 6.73 (d, 2H), 3.96 (t, 2H), 3.64 (s, 3H), 3.6-3.55 (m, 3H), 2.73 (t, 2H), 2.3 (t, 2H), 1.99 (m, 2H), 1.5-1.3 (m, 3H).



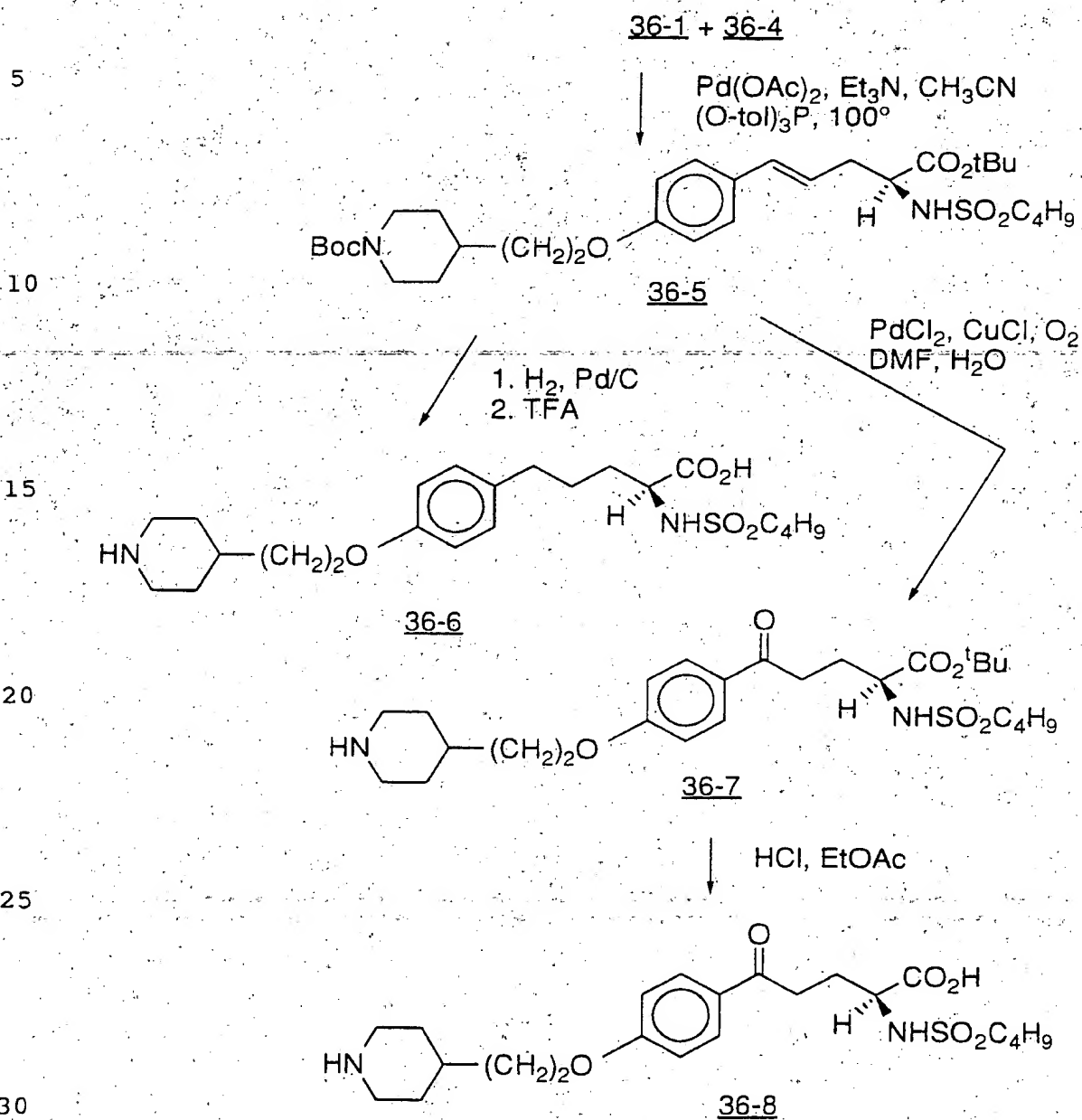
tert-Butyl 2(S)-Phenylsulfonylaminopent-4-enoate (35-11)

This compound was prepared using the procedure described for 36-4, using phenylsulfonyl chloride as the sulfonylating agent.

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SCHEME 36

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SCHEME 36 (CONT'D)

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1-Bromo-4-[2-(N-Boc-piperidin-4-yl)ethyloxy]benzene (36-1)

A mixture of 1-4 (6.45g, 19.0 mmol), 4-bromophenol (3.29g, 19 mmol), and Cs₂CO₃ (3.10g, 9.5 mmol) in 50 mL of DMF was stirred at room temperature for 18 hr. The solution was then diluted with 200 mL ethyl acetate and washed with H₂O (4 x 100 mL), then dried over Na₂SO₄, filtered and concentrated. Flash chromatography (silica, 30% EtOAc/hexanes) gave 36-1 as a white solid.

TLC R_f = 0.45 (silica, 30% EtOAc/hexanes)

¹H NMR (300 MHz, CDCl₃) δ 7.34 (d, J = 10 Hz, 2H), 6.78 (d, J = 10 Hz, 2H); 4.18 (bn, d, 2H), 3.97 (t, J = 6 Hz, 2H); 2.73 (bnM, 2H), 1.76 (m, 6H), 1.48 (s, 9H), 1.08 (m, 2H).

tert-Butyl 2(S)-Aminopent-4-enoate (36-3)

Liquid isobutylene (100 mL) was slowly added to 36-2 (4.0g, 34.7 mmol) in a mixture of dioxane (100 mL) and concentrated sulfuric acid (1.5 mL) in a 500 mL pressure bottle. The bottle was sealed and the contents stirred at room temperature for 48 hr. The solution was poured into an ice-cold mixture of ethyl acetate (120 mL) and 1N NaOH (120 mL). The organic layer was removed and the basic aqueous layer extracted with ethyl acetate (2 x 100 mL). The pooled organic extracts were dried over Na₂SO₄ and evaporated to give 36-3 as a colorless oil.

¹H NMR (300 MHz, CDCl₃) δ 5.75 (m, 1H), 5.19 (d, J = 7.5 Hz, 1H), 5.13 (s, 1H), 3.45 (m, 1H), 2.58-2.32 (m, 2H), 1.65 (br, s, 1H), 1.41 (s, 9H).

tert-Butyl 2(S)-n-Butylsulfonylaminopent-4-enoate (36-4)

A mixture of 36-3 (809 mg, 4.73 mmol) and N-methylmorpholine (0.60 mL, 5.46 mmol) in CH₂Cl₂ (15 mL) was cooled to 0°C under Argon. N-Butyl sulfonyl chloride (0.66 mL, 5.10 mmol) was added and the mixture was allowed to warm to room temperature and stirred for 12 hr. The solution was washed with 10% citric acid

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H₂O, sat. NaHCO₃ and brine (10 mL each) then dried over Na₂SO₄ filtered and concentrated to give 36-4 as a straw-colored oil.

¹H NMR (300 MHz, CDCl₃) δ 5.73 (m, 1H), 5.19 (d, J = 7.5 Hz, 1H), 5.13 (s, 1H), 4.93 (d, J = 6.8 Hz, 1H), 4.15 (m, 1H), 3.01 (t, J = 6.3 Hz, 2H), 2.52 (m, 2H), 1.82 (m, 2H), 1.41 (s, 9H), 0.96 (t, 3H).

tert-Butyl 2(S)-n-Butylsulfonylamino-5-[4-(2-N-Boc-piperidin-4-yl)-ethyloxyphenyl]pent-4-enoate (36-5)

A mixture of 36-4 (402 mg, 1.05 mmol), 36-1 (361 mg, 1.18 mmol), palladium (II) acetate (24.0 mg, 0.10 mmol), triethylamine (0.29 ml, 1.99 mmol), tri-*o*-tolylphosphine (91 mg, 0.33 mmol), and CH₃CN (5 ml) was placed in a sealed tube and heated at 100° for 18 hr. The solvent was evaporated and the residue subjected to flash chromatography (silica, 30% EtOAc/hexanes) to give 36-5 as a pale yellow oil.

¹H NMR (300 MHz, CDCl₃) δ 7.25 (d, J = 11 Hz, 2H), 6.85 (d, J = 11 Hz, 2H), 6.41 (d, J = 13 Hz, 1H), 5.95 (m, 1H), 4.93 (d, J = 6 Hz, 1H), 4.2 - 3.95 (m, 6H), 2.98 (m, 2H), 2.81 (m, 4H), 1.81 (m, 7H), 1.50 (s, 9H), 1.43 (s, 9H), 1.12 (m, 2H), 0.95 (m, 3H).

2(S)-n-Butylsulfonylamino-5[4-(2-N-Boc-piperidin-4-yl)ethyloxy-phenyl]pentanoic acid (36-6)

A solution of 36-5 (184 mg, 0.30 mmol) in 50 mL CH₃OH was treated with 24 mg of 10% Pd on C and hydrogenated on a Parr apparatus at 40 psi for 12 hr. The catalyst was removed by filtration through a bed of celite and the solution concentrated to give a colorless oil. This material was dissolved in 5 mL CH₂Cl₂, cooled to 0° C and treated with TFA (2 mL). After stirring for 3 hr, the solvent was removed and the residue purified by reverse phase chromatography giving 36-6 as a white solid, following lyophilization.

¹H NMR (300 MHz, D₂O) δ 7.08 (d, J = 11 Hz, 2H), 6.81 (d, J = 11 Hz, 2H), 3.98 (m, 4H), 3.47 (d, J = 12 Hz, 2H), 3.01 (m, 2H), 2.85-2.61 (m, 6H), 1.8-1.6 (m, 7H), 1.15 (m, 2H), 0.96 (m, 3H).

tert-Butyl 2(S)-n-Butylsulfonylamino-5-[4-(2-N-Boc-piperidin-4-yl)-ethyloxyphenyl]-5-oxopentanoate (36-7)

Oxygen was bubbled into a mixture of CuCl (10 mg, 0.11 mmol), PdCl₂ (6.0 mg, 0.03 mmol), and 5 ml of DMF which contained 10% H₂O. After 0.5 hr., a solution of 36-5 in aqueous DMF (1.5 ml) was added and the mixture stirred under an O₂ atmosphere for 12 hr. The reaction was quenched by the addition of 10% KHSO₄ (3 ml) and extracted with CH₂Cl₂ (2 x 20 ml). The pooled CH₂Cl₂ extracts were dried (MgSO₄) concentrated and chromatographed (silica, 50% EtOAc/hexanes) to give 36-7 as a colorless glass. FAB MS, 611 (M+1). ¹H NMR (300 MHz, CDCl₃) δ 7.95 (d, J = 11 Hz, 2H), 6.95 (d, J = 11 Hz, 2H), 5.13 (d, J = 7 Hz, 1H), 4.15 (m, 5H), 3.20 (m, 2H), 2.98 (m, 2H), 2.71 (m, 2H), 2.28 (m, 1H), 1.98 (m, 1H), 1.81 (m, 5H), 1.52 (s, 9H), 1.48 (s, 9H), 1.23 (m, 2H), 0.98 (m, 3H).

2 (S)-n-Butylsulfonylamino-5-[4-2-piperidin-4-yl)ethyloxyphenyl]-5-oxopentanoic acid (36-8)

A solution of 36-7 (64 mg, 0.105 mmol) in 10 ml EtOAc was cooled to -10°C and HCl gas introduced for 10 min. After stirring at -10°C for 2 hr the solution was evaporated and the residue purified by reverse phase chromatography (C18 column, 0.1% TFA/CH₃CN gradient) to give 36-8 as a white powder, following lyophilization. ¹H NMR (300 MHz, D₂O) 7.78 (d, J = 11 Hz, 2H), 6.85 (d, J = 11 Hz, 2H), 4.08 (m, 2H), 3.85 (m, 1H), 3.26 (d, J = 13.8 Hz, 2H), 3.01-2.8 (m, 6H), 2.08 (m, 2H), 1.80 (d, J = 14 Hz, 2H), 1.68 (m, 1H), 1.60 (m, 2H), 1.46 (m, 2H), 1.35 (m, 2H), 1.08 (m, 2H), 0.81 (m, 3H).

Therapeutic Treatment

Compounds of the invention may be used for inhibiting integrin protein-complex function relating to cell attachment activity. They may be administered to patients where inhibition of human or mammalian platelet aggregation or adhesion is desired. Thus, they may find utility in surgery on peripheral arteries (arterial grafts, carotid endarterectomy) and in cardiovascular surgery where manipulation of

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arteries and organs, and/or the interaction of platelets with artificial surfaces, leads to platelet aggregation and consumption. The aggregated platelets may form thrombi and thromboemboli. Compounds of the invention may be administered to these surgical patients to prevent the formation of thrombi and thromboemboli.

These compounds may be administered by any convenient means which will result in its delivery into the blood stream in substantial amount including continuous intravenous or bolus injection or oral methods. Compositions of the invention include compounds of the invention and pharmaceutically acceptable carriers, e.g. saline, at a pH level of for example 7.4, suitable for achieving inhibition of platelet aggregation. They may also be used in combination with anticoagulants such as heparin or warfarin. Intravenous or oral administration are presently contemplated as the preferred administration routes.

In one exemplary application, a suitable amount of compound is intravenously administered to a heart attack victim undergoing angioplasty. Administration occurs during or several minutes prior to angioplasty, and is in an amount sufficient to inhibit platelet aggregation, e.g. an amount which achieves a steady state plasma concentration of between about 0.01-30 μ M, preferably between about 0.03-3 μ M. When this amount is achieved, an infusion of between about 0.1-100 μ g per kilo per min., preferably between about 1-20 μ g per kilo per min., most preferably 1-10 μ g per kilo per min. is maintained to inhibit platelet aggregation. Advantageously, compounds of the present invention may be administered in divided doses of two, three, or four times daily. Should the patient need to undergo bypass surgery, administration may be stopped immediately and will not cause complications during surgery that would be caused by other materials such as aspirin or monoclonal antibodies.

Furthermore, preferred compounds for the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using those forms of transdermal skin patches well known to those of ordinary skill in that art. To be administered in the form of a transdermal delivery system,

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the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regime.

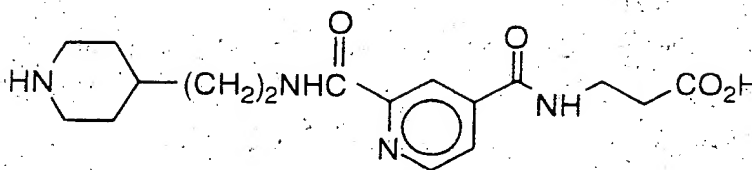
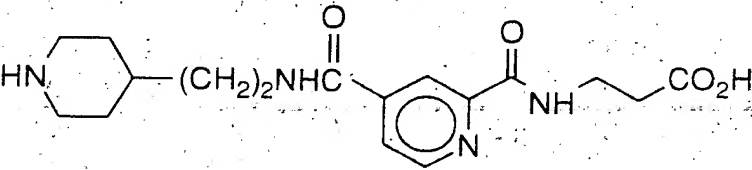
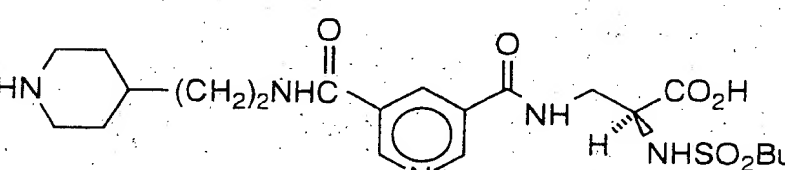
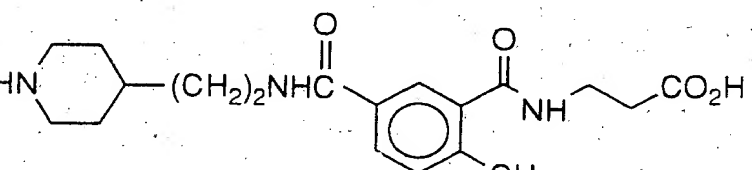
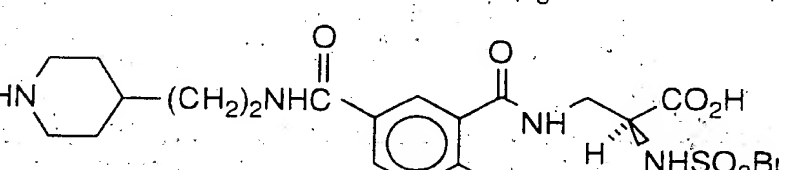
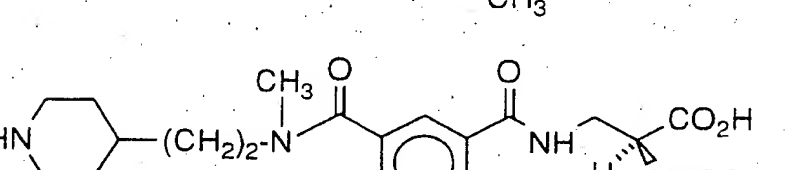
Oral dosages of the present invention, when used for the indicated effects, will range between about 0.01 mg per kg of body weight per day (mg/kg/day) to about 500 mg/kg/day and preferably 1.0-400 mg/kg/day and most preferably 1-300 mg/kg/day. The present invention also includes a pharmaceutical composition comprising compounds of the present invention and tissue type plasminogen activator or streptokinase. The invention also includes a method for promoting thrombolysis and preventing reocclusion in a patient which comprises administering to the patient an effective amount of compositions of the invention.

The present invention may be embodied in other specific forms without departing from the spirit or essential attributes thereof. Thus, the specific examples described above should not be interpreted as limiting the scope of the present invention.

Using the methods previously described, the following preferred compounds were prepared and evaluated:

EXHIBIT 2

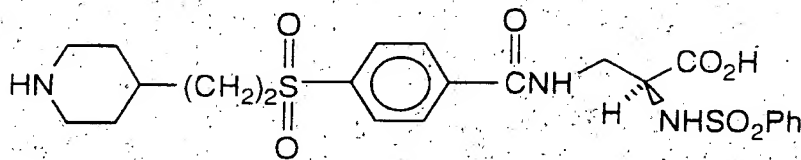
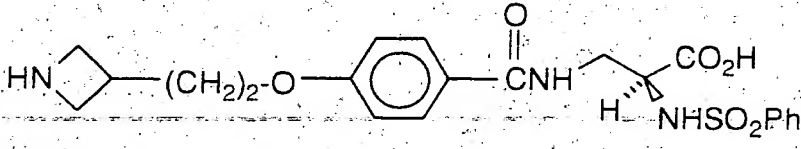
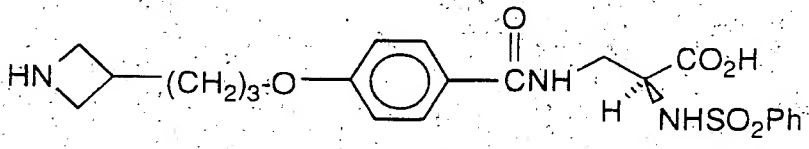
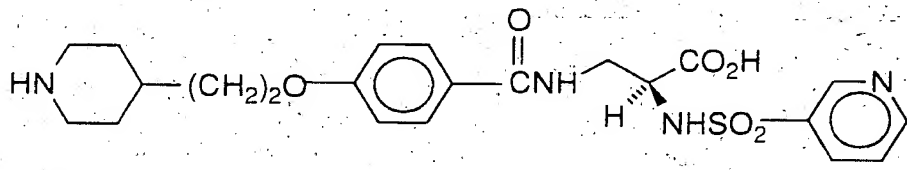
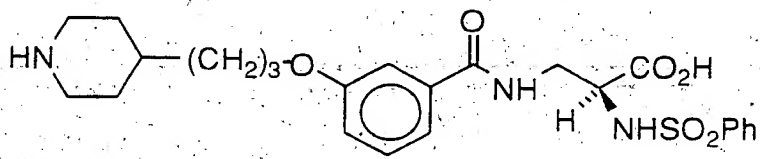
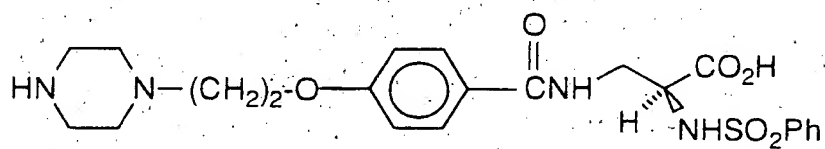
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| | <u>Compound</u> | <u>IC₅₀ (μM) Inhibition of Platelet Aggregation</u> |
|----|--|--|
| 5 |  | 1.6 |
| 10 |  | 1.1 |
| 15 |  | 0.11 |
| 20 |  | 0.45 |
| 25 |  | 0.15 |
| 30 |  | 0.023 |

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| | <u>Compound</u> | <u>IC₅₀ (μM) Inhibition of Platelet Aggregation</u> |
|----|-----------------|--|
| 5 | | 0.14 |
| 10 | | 0.020 |
| 15 | | 0.017 |
| 20 | | 0.052 |
| 25 | | 0.15 |
| 30 | | 0.009 |

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| | <u>Compound</u> | <u>IC₅₀ (μM) Inhibition of Platelet Aggregation</u> |
|----|--|--|
| 5 |  | 0.019 |
| 10 |  | 0.017 |
| 15 |  | 0.01 |
| 20 |  | 0.009 |
| 25 |  | 0.056 |
| 30 |  | 0.023 |

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While the invention has been described and illustrated in reference to certain preferred embodiments thereof, those skilled in the art will appreciate that various changes, modification and substitutions can be made therein without departing from the spirit and the scope of the invention. For example, effective dosages other than the preferred doses as set forth hereinabove may be applicable as a consequence of variations in the responsiveness of the mammal being treated for severity of clotting disorders or emboli, or for other indications for the compounds of the invention indicated above. Likewise, the specific pharmacological responses observed may vary according to and depending upon the particular active compound selected or whether there are present pharmaceutical carriers, as well as the type of formulation and mode of administration employed, and such expected variations or differences in the results are contemplated in accordance with the objects and practices of the present invention. It is intended, therefore, that the invention be limited only by the scope of the claims which follow and that such claims be interpreted as broadly as is reasonable.

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WHAT IS CLAIMED IS:

1. A compound of the formula

5



and the pharmaceutically acceptable salts thereof wherein:

10

Aryl is a 6-membered monocyclic aromatic ring system containing 0, 1, 2, 3 or 4 N atoms, and either unsubstituted or substituted with R⁵;

X is

15

20

25

30

NR² NR³

-NR¹R², -NR¹-C-R¹, -C-NHR⁴,
 NR²
 -NR¹-C-NR³R⁴, or a 4- to 10- membered mono- or polycyclic aromatic or nonaromatic ring system containing 0, 1, 2, 3 or 4 heteroatoms selected from N, O and S and either unsubstituted or substituted with R¹, R², R³, or R⁴, wherein R¹, R², R³ and R⁴ are independently selected from the group consisting of hydrogen, C₁-10 alkyl, C₃-8 cycloalkyl, aryl C₀-8 alkyl, amino C₀-8 alkyl, C₁-3 acylamino C₀-8 alkyl, C₁-6 alkylamino C₀-8 alkyl, C₁-6 dialkylamino C₀-8 alkyl, C₁-4 alkoxy C₀-6 alkyl, carboxy C₀-6 alkyl, C₁-3 alkoxycarbonyl C₀-6 alkyl, carboxy C₀-6 alkyloxy and hydroxy C₀-6 alkyl;

Y is

C₀-8 alkyl, C₄-10 cycloalkyl,
 C₀-8 alkyl-NR³-CO-C₀-8 alkyl,
 C₀-8 alkyl-CONR³-C₀-8 alkyl,

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C0-8 alkyl-O-C0-8 alkyl,
 C0-8 alkyl-SO_n-C0-8 alkyl,
 (CH₂)₀₋₈aryl(CH₂)₀₋₈,
 (CH₂)₀₋₆aryl-SO_n-
 (CH₂)₀₋₈aryl-CO-(CH₂)₀₋₈,
 (CH₂)₀₋₆aryl-SO₂-(CH₂)₀₋₆,
 (CH₂)₀₋₆-NR³-(CH₂)₀₋₆,
 (CH₂)₀₋₆-aryl-CH(OH)-(CH₂)₀₋₆,
 (CH₂)₀₋₈aryl-CONH-(CH₂)₀₋₈,
 C0-8 alkyl-SO₂-NR³-C0-8 alkyl-,
 C0-8 alkyl-CO-C0-8 alkyl, or
 C0-8 alkyl-CH(OH)-C0-8-alkyl
 where n is an integer from 0-2,

Z and A are independently chosen from:

(CH₂)_m, (CH₂)_mO(CH₂)_n, (CH₂)_mNR³(CH₂)_n,
 $\begin{array}{ccc} \text{O} & & \text{O} \\ | & & | \end{array}$
 (CH₂)_mCNR³(CH₂)_n, (CH₂)_mNR³C(CH₂)_n,
 $\begin{array}{ccc} \text{O} & & \text{S} \end{array}$
 (CH₂)_mC(CH₂)_n, (CH₂)_mC(CH₂)₂, (CH₂)_mSO₂(CH₂)_n
 (CH₂)_mS(CH₂)_n, (CH₂)_mSO(CH₂)_n,
 (CH₂)_mSO₂NR³(CH₂)_n, (CH₂)C=C(CH₂)_n, and
 (CH₂)_mCH(OH)(CH₂)_n

where m and n are integers independently chosen from 0-6;
 provided that when A is (CH₂)_m, the Aryl ring bonded by Z and A,
 must contain at least one heteroatom;

R⁵ is

hydrogen,
 C1-6 alkyl,
 C0-6 alkylcarboxy C0-6 alkyl,
 C0-6 alkyloxy C0-6 alkyl,
 hydroxy C0-6 alkyl,

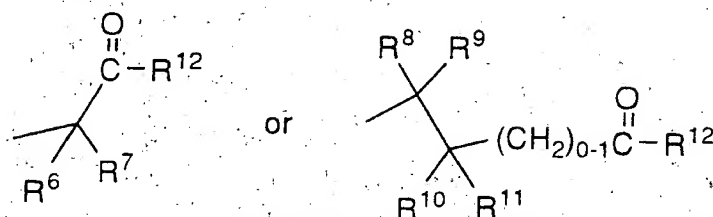
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aryl C0-6 alkyl, or
halogen;

B is

5

10



wherein R6, R7, R8, R9, R10, and R11 are independently chosen from:

15

20

25

30

hydrogen, fluorine, hydroxy C1-6 alkyl,
carboxy C0-6 alkyl,
C1-8 alkyl, hydroxyl, C1-6 alkyloxy, aryl-
C0-6alkyloxy,
C3-8 cycloalkyl,
aryl C0-6 alkyl, C1-6 alkylcarbonyloxy,
C0-6 alkylamino C0-6 alkyl, aryl C0-6
alkylamino C0-6alkyl,
C0-6 dialkylamino C0-6 alkyl,
C0-6 alkylaminocarbonyloxy, aryl C0-6
alkylaminocarbonyloxy,
C1-8 alkylsulfonylamino C0-6 alkyl,
aryl C0-6 alkylsulfonylamino C0-6 alkyl,
C1-8 alkyloxycarbonylamino C0-8 alkyl,
aryl C0-8 alkyloxycarbonylamino C0-8 alkyl,
C1-8 alkylcarbonylamino C0-6 alkyl,
aryl C0-6 alkylcarbonylamino C0-6 alkyl,
C0-8 alkylaminocarbonylamino C0-6 alkyl,
aryl C0-8 alkylaminocarbonylamino C0-6 alkyl,
C0-8 alkylaminosulfonylamino C0-6 alkyl,

aryl C0-8 alkylaminosulfonylamino C0-6 alkyl,
 C1-6 alkylsulfonyl C0-6 alkyl,
 aryl C0-6 alkylsulfonyl C0-6 alkyl,
 C1-6 alkylcarbonyl C0-6 alkyl,
 5 aryl C0-6 alkylcarbonyl C0-6 alkyl,
 C0-8alkylaminocarbonyl C0-8 alkyl,
 aryl C0-8 alkylaminocarbonyl C0-8 alkyl,
 C0-8 alkylaminosulfonyl C0-8 alkyl, and
 10 aryl C0-8 alkylaminosulfonyl C0-8 alkyl,
 wherein groups may be unsubstituted or substituted with one or more
 substituents selected from R1 and R2; and

R12 is chosen from:

15 hydroxy,
 C1-8 alkyloxy,
 aryl C0-6 alkyloxy,
 C1-8 alkylcarbonyloxy C1-4 alkyloxy,
 20 aryl C1-8 alkylcarbonyloxy C1-4 alkyloxy, and
 an L- or D-amino acid joined by an amide linkage and
 wherein the carboxylic acid moiety of said amino acid is as
 the free acid or is esterified by C1-6 alkyl.

2. A compound of Claim 1 having the formula



and the pharmaceutically acceptable salts thereof wherein aryl is a 6-
 30 membered aromatic ring system containing 0, 1, 2, or 3 N atoms,

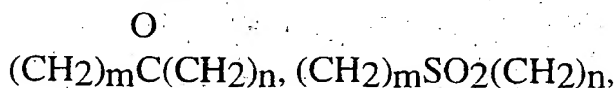
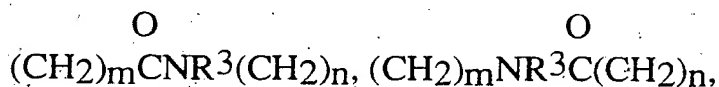
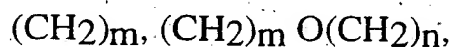
X is
$$\begin{array}{c} \text{NR}^2 \quad \text{NR}^3 \\ -\text{NR}^1\text{R}^2, -\text{NR}^1-\text{C}-\text{R}^1, -\text{C}-\text{NHR}^4, \\ \text{NR}^2 \\ -\text{NR}^1-\text{C}-\text{NR}^3\text{R}^4, \text{ or a 4- to 10- membered mono- or} \end{array}$$

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polycyclic aromatic or nonaromatic ring system containing
 0, 1, 2, 3 or 4 heteroatoms selected from N, O and S and
 either unsubstituted or substituted with R¹, R², R³ or R⁴,
 wherein R¹, R², R³ and R⁴ are independently selected
 from the group consisting of hydrogen,
 C₁-10 alkyl, C₃-8 cycloalkyl,
 aryl C₀-8 alkyl,
 amino C₀-8 alkyl, C₁-3 acylamino C₀-8 alkyl,
 C₁-6 alkylamino C₀-8 alkyl,
 C₁-6 dialkylamino C₀-8 alkyl,
 C₁-4 alkoxy C₀-6 alkyl,
 carboxy C₀-6 alkyl, C₁-3 alkoxycarbonyl C₀-6
 alkyl,
 carboxy C₀-6 alkyloxy, or
 hydroxy C₀-6 alkyl;

Y is C₀-8 alkyl,
 C₀-8 alkyl-NR³-CO-C₀-8 alkyl,
 C₀-8 alkyl-CONR³-C₀-8 alkyl,
 C₀-8 alkyl-O-C₀-8 alkyl,
 C₀-8 alkyl-aryl-C₀-8 alkyl,
 C₀-8 alkyl-S(O_n)-C₀-8 alkyl,
 C₀-8 alkyl-SO₂-NR³-C₀-8 alkyl-, or
 C₀-8 alkyl-CO-C₀-8 alkyl,
 where n is an integer from 0-2;

Z and A are independently chosen from:

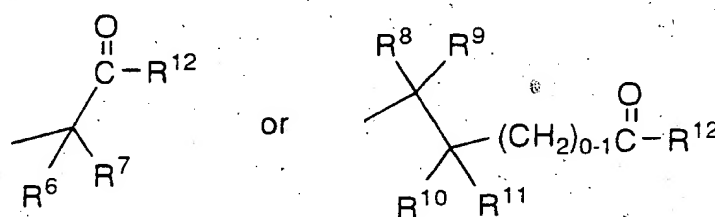


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 $(\text{CH}_2)_m\text{SO}_2\text{NR}^3(\text{CH}_2)_n$, and $(\text{CH}_2)_m\text{NR}^3\text{SO}_2(\text{CH}_2)_n$,

where m and n are integers independently chosen from 0-6;
 provided that when A is $(\text{CH}_2)_m$ the Aryl ring, bounded by Z and A,
 must contain at least one heteroatom;

B is



wherein R6, R7, R8, R9, R10 and R11 are independently chosen from:

hydrogen, fluorine
 C1-8 alkyl,
 C3-8 cycloalkyl,
 aryl C0-6 alkyl,
 C0-6 alkylamino C0-6 alkyl,
 aryl C0-6 alkylamino C0-6 alkyl,
 C0-6 dialkylamino C0-6 alkyl,
 C1-8 alkylsulfonylamino C0-6 alkyl,
 aryl C0-6 alkylsulfonylamino C0-6 alkyl,
 C1-8 alkyloxycarbonylamino C0-8-alkyl,
 aryl C0-8 alkylcarbonylamino C0-8 alkyl,
 C1-8 alkylcarbonylamino C0-6 alkyl,
 C0-8 alkylaminocarbonylamino C0-6 alkyl,
 aryl C0-8 alkylaminocarbonylamino C0-6 alkyl,
 C0-8 alkylaminosulfonylamino C0-6 alkyl,
 aryl C0-8 alkylaminosulfonylamino C0-6 alkyl,
 C1-6 alkylsulfonyl C0-6 alkyl,
 aryl C0-6 alkylsulfonyl C0-6 alkyl,

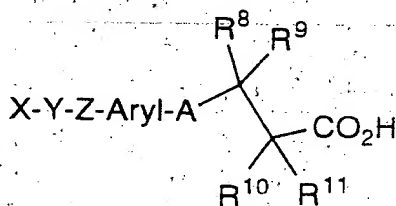
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C1-6 alkylcarbonyl C0-6 alkyl,
 aryl C0-6 alkylcarbonyl C0-6 alkyl; and
 C0-8 alkylaminocarbonyl C0-8 alkyl,
 aryl C0-8 alkylaminocarbonylamino C0-8 alkyl,

R12 is chosen from:

hydroxy,
 C1-8 alkyloxy,
 aryl C0-6 alkyloxy,
 C1-8 alkylcarbonyloxy C1-4 alkyloxy, and
 aryl C1-8 alkylcarbonyloxy C1-4 alkyloxy.

3. A compound of Claim 2 having the formula



and the pharmaceutically acceptable salts thereof wherein aryl is a 6-membered monocyclic aromatic ring system containing 0, 1 or 2 N atoms,

NR3

X is -NR1R2, -C-NHR4, or a 4- to 8-membered aromatic or nonaromatic ring system containing 0, 1, 2 or 3 heteroatoms selected from N and O wherein R1, R2, R3 and R4 are independently selected from the group consisting of hydrogen,

C1-10 alkyl,
 aryl C0-8 alkyl,
 carboxy C0-6 alkyl,

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hydroxy C0-6 alkyl,
 amino C0-8 alkyl, or
 C1-6 alkylamino C0-8 alkyl;

5 Y is C0-8 alkyl,
 C0-8 alkyl-NR³-CO-C0-8 alkyl,
 C0-8 alkyl-CONR³-C0-8 alkyl,
 C0-8 alkyl-O-C0-8 alkyl,
 10 C0-8 alkyl-S(O_n)-C0-8 alkyl, or
 C0-8 alkyl-aryl-C0-8 alkyl;

Z and A are independently chosen from:

15 (CH₂)_m NHCO(CH₂)_n, (CH₂)_m,
 (CH₂)_m O(CH₂)_n, (CH₂)_m, CONH(CH₂)_n,
 (CH₂)_mSO₂(CH₂)_n, (CH₂)_m, CO(CH₂)_n,

wherein m and n are integers from 0-6; and provided that when A is
 20 (CH₂)_m the Aryl ring, bounded by Z and A must contain at least one
 heteratom; and

R⁸, R⁹, R¹⁰ and R¹¹ are independently chosen from:

25 hydrogen, fluorine,
 C1-8 alkyl,
 C3-8 cycloalkyl,
 aryl C0-6 alkyl,
 C0-6 alkylamino C0-6 alkyl,
 C0-6 dialkylamino C0-6 alkyl,
 30 C1-8 alkylsulfonylamino C0-6 alkyl,
 aryl C0-6 alkylsulfonylamino C0-6 alkyl,
 C1-8 alkyloxycarbonylamino C0-8 alkyl,
 aryl C0-8 alkyloxycarbonylamino C0-8 alkyl,
 C1-8 alkylcarbonylamino C0-6 alkyl,

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5 aryl C0-6 alkylcarbonylamino C0-6 alkyl,
C0-8 alkylaminocarbonylamino C0-6 alkyl,
aryl C0-8 alkylaminocarbonylamino C0-6alkyl,
C0-8 alkylaminosulfonylamino C0-6 alkyl,
aryl C0-8 alkylaminosulfonylamino C0-6alkyl,
C1-6 alkylsulfonyl C0-6 alkyl,
aryl C0-6 alkylsulfonyl C0-6 alkyl,
C1-6 alkylcarbonyl C0-6 alkyl, and
10 aryl C0-6 alkylcarbonyl C0-6 alkyl.

4. A compound of Claim 3, and pharmaceutical salts thereof, selected from the group consisting of:

15 N-2-(4-Piperidinyloethyl)-N'-(2-carboxyethyl)-1,3-benzenedicarboxamide;

N-2-(4-Piperidinyloethyl)-N'-[3-(2-fluoro)propanoic-acid]-1,3-benzenedicarboxamide;

20 {N-2-(4-Piperidinyloethyl)-N'-3-[3(R)-phenethylpropanoic acid]}-1,3-benzenedicarboxamide;

25 {N-[2-(4-Piperidinyloethyl)-N'-3-[3(R)-indolylethylpropanoic acid]}-1,3-benzenedicarboxamide;

N-(4-Piperidinylmethyl)-N'-3-[2(S)-n-butylsulfonylaminopropionic acid]-1,3-benzenedicarboxamide;

30 N-(4-Piperidinylmethyl)-N'-[(2-carboxyethyl)-1,3-benzenedicarboxamide];

N-2-(4-Piperidinyl)ethyl-N'-(2-carboxyethyl)-2-methyl-1,3-benzenedicarboxamide;

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3-[(4-Piperidiny)methoxy]-N-(2-carboxyethyl)phenylacetamide;

4-(Piperidin-4-yl)phenyl-3-propionyl-[2(S)-n-butylsulfonylamino]- β -alanine;

4-[(1,2,5,6-Tetrahydropyridin-4-yl)phenyl-3-propionyl-[2(S)-n-butylsulfonylamino]- β -alanine;

3-[3-(Piperidin-4-ylmethyl)phenyl]propionyl- β -alanine;

3-[4-(1,2,5,6-Tetrahydropyridin-4-yl)butyryl]- β -alanine;

{N-2-(4-Piperidinylethyl)-N'-3-[2(S)-n-butylsulfonylaminopropionic acid]}-1,3-benzenedicarboxamide;

N-2-(4-Piperidiny)ethyl-N'-3-[2(S)-n-butylsulfonylaminopropionic acid]-2-methyl-1,3-benzenedicarboxamide;

{N-[2-(4-Piperidiny)ethyl]-N-(phenethyl)}-N'-(2-carboxyethyl)-1,3-benzenedicarboxamide;

N-[2-(4-Piperidiny)ethyl-N-propyl]-N'-(2-carboxyethyl)-1,3-benzenedicarboxamide;

N-2-(4-Piperidiny)ethyl-N'-[3-(2(S)-hexanoylaminopropionic acid)]-1,3-benzenedicarboxamide;

[N-2-(4-Piperidiny)ethyl]-N'-[3-2(S)-thien-2-yl-sulfonylamino-propionic acid]-1,3-benzenedicarboxamide;

4-methyl-N-[2-(4-piperidiny)ethyl]-N'-2-(carboxyethyl)-1,3-benzenedicarboxamide;

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3-[(2-Carboxyethyl)aminosulfonyl]-N-[2-(4-piperidinylethyl)]-benzamide;

5 3-[2-(4-Piperidinyl)ethylaminosulfonyl]-N-[(2-carboxyethyl)]-benzamide;

3-[(4-Piperidinyl)methylaminosulfonyl]-N-[(2-carboxyethyl)]-benzamide;

10 N-[(2-(4-Piperidinyl)ethyl)-N'-[(2-carboxyethyl)-3,5-pyridinedicarboxamide];

15 N-[2-(4-Piperidinyl)ethyl]-N'-[(2-carboxy)ethyl]-2,6-pyridinedicarboxamide;

3-(3-Carboxypropyloxy)-N-(4-piperidinylmethyl)carboxamide;

20 N-2-(4-Piperidinylethyl)-N'-3-(2-benzylpropionic acid)-1,3-benzenedicarboxamide;

3-(4-Carboxybutanoyl)-N-(4-piperidinylmethyl)benzenecarboxamide;

3-(5-Carboxypentanoyl)-N-(4-piperidinylmethyl)benzenecarboxamide;

25 4-(Piperidin-4-yl)phenyl-3-propionyl- β -alanine;

4-(1,2,5,6-Tetrahydropyridin-4-yl)phenyl-3-propionyl- β -alanine;

30 6-[2-(Piperidin-4-yl)ethyloxy]nicotinamide-N-[3-(2(S)-phenylsulfonylamino)propionic acid];

3-Chloro-4-[2-(Piperidin-4-yl)ethyloxy]phenylcarbonyl-2(S)-phenylsulfonylamino- β -alanine;

4-[3-(Piperidin-3-yl)propyloxy]-N-[3-(2(S)-butylsulfonylamino)-propionic acid]benzamide;

4-[2-(Piperidin-4-yl)ethyloxy]phenylcarboxyl-2-(S)-hydroxy- β -alanine.

N-[3-(2(S)-Phenylsulfonylamino)propionate]-4'-aminomethyl-4-biphenylcarboxamide;

N-[3-(2(S)-Phenylsulfonylamino)propionate]-4'-amidino-4-biphenylcarboxamide;

4-[3-(Pyridin-4-yl)propyloxy]benzoyl-2(S)-phenylsulfonylamino- β -alanine;

4-[3-(Piperidin-4-yl)propyl]benzoyl-2(S)-phenylsulfonylamino- β -alanine;

4-[2-(Piperidin-4-yl)oxyethyloxy]benzoyl-2(S)-phenylsulfonylamino- β -alanine;

4-N-(Piperazinyl)benzoyl-2(S)-phenylsulfonylamino- β -alanine;

4-[2-(N,N-Diethylamino)ethyloxy]benzoyl-2(S)-phenylsulfonylamino- β -alanine;

4-[4-(N-Morpholino)butyloxy]benzoyl-2(S)-phenylsulfonylamino- β -alanine;

4-[2-(N-Benzylimidazol-4-yl)ethyloxy]benzoyl-2(S)-phenylsulfonylamino- β -alanine;

4-[2-(Imidazol-4-yl)ethyloxy]benzoyl-2(S)-phenylsulfonylamino- β -alanine;

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4-[3-(1-Methylimidazol-4-yl)propyloxy]benzoyl-2(S)-phenylsulfonyl-
amino- β -alanine methyl ester;

5 4-[3-(1-Methylimidazol-4-yl)propyloxy]benzoyl-2(S)-phenylsulfonyl-
amino- β -alanine;

4-[3-(1-Imidazolyl)propyloxy]benzoyl-2(S)-phenylsulfonylamino- β -
alanine t-butyl ester;

10 4-[3-(1-Imidazolyl)propyloxy]benzoyl-2(S)-phenylsulfonylamino- β -
alanine;

4-[2-(Pyrrolidinyl)ethyloxy]benzoyl-2(S)-phenylsulfonylamino- β -
alanine;

15 2(S)-Phenylsulfonylamino-4-(4-piperazinylphenoxy)butanoic acid;

t-Butyl 2(S)-t-Butyloxycarbonylamino-4-[4-N-methylpiperazinyl]-
phenoxy]butanoate;

20 2(S)-Amino-3-[4-(N-methylpiperazinyl)phenoxy]butanoic acid;

2(S)-3-Pyridylsulfonylamino-4-[4-(N-methylpiperazinyl)phenoxy]-
butanoic acid;

25 4-[(4-Pyrrolidinylbut-2-enyl)oxy]benzoyl-2(S)-phenylsulfonylamino- β -
alanine t-butyl ester;

30 4-[(4-Pyrrolidinylbut-2-enyl)oxy]benzoyl-2(S)-phenylsulfonylamino- β -
alanine;

3-[(Piperidin-4-ylmethyl)aminocarbonyl]benzoyl-2(S)-3-pyridyl-
sulfonylamino- β -alanyl-glycine;

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4-[(2-Aminoethyl)aminocarbonyl]benzoyl-2-(S)-phenylsulfonylamino- β -alanine;

5 4-[(2-Guanidinoethyl)aminocarbonyl]benzoyl-2(S)-phenylsulfonylamino- β -alanine;

4-[(4-N-Methylaminobutyl)aminocarbonyl]benzoyl-2(S)-3-pyridylsulfonylamino- β -alanine;

10 {N-2-(4-Piperidinylethyl)-N'-3-[ethyl 2(S)-n-butylsulfonylamino-propanoate]}-1,3-benzenedicarboxamide;

15 4-[2-(4-Piperidinyl)ethyloxy]-N-[3-(2(S)-n-butylsulfonylamino)-propionate]benzamide;

4-[2-(4-Piperidinyl)ethyloxy]-N-[3-(2(S)-n-phenylsulfonylamino)-propionate]benzamide;

20 2(S)-Phenylsulfonylamino-5-[4-(3-(1-methylimidazol-4-yl)propyloxy-phenyl)]pentanoic acid;

2(S)-n-Butylsulfonylamino-5-[4-2-(piperidin-4-yl)ethyloxyphenyl]-5-oxopentanoic acid;

25 N-2-(4-Piperidinylethyl)-N'-3-[2(S)-(3-pyridylsulfonylamino)-propanoic acid]-1,4-benzenedicarboxamide;

30 N-3-(4-Piperidinylpropyl)-N'-3-[2(S)-(3-pyridylsulfonylamino)-propanoic acid]-1,4-benzenedicarboxamide;

4-[2-(Azetidin-3-yl)ethyloxy]benzoyl-2(S)-phenylsulfonylamino- β -alanine;

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4-[3-(Azetidin-3-yl)propyloxy]benzoyl-2(S)-phenylsulfonylamino- β -alanine; and

3-[(4-Piperidinyl)methyloxy]-N-[3-(2-indol-3-yl)ethyl-propionic acid]phenyl acetamide.

5. A method of blocking fibrinogen from acting at its platelet receptor site in a mammal, including a human comprising administering a pharmacologically effective amount of a compound as claimed in Claim 1.

6. A method of preventing thrombus and embolus formation in a mammal, including a human, in need thereof, comprising administering a pharmacologically effective amount of a compound as claimed in Claim 1.

7. A method of treating thrombus and embolus formation in a mammal, including a human, in need thereof, comprising administering a pharmacologically effective amount of a compound as claimed in Claim 1.

8. A method of inhibiting aggregation of blood platelets in a mammal, including a human, comprising administering a pharmacologically effective amount of a compound as claimed in Claim 1.

9. A method of blocking fibrinogen from acting at its platelet receptor site in a mammal, including a human comprising administering a pharmacologically effective amount of a compound of Claim 4.

10. A method of preventing thrombus and embolus formation in a mammal, including a human, in need thereof, comprising administering a pharmacologically effective amount of compound of Claim 4.

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11. A method of treating thrombus and embolus formation in a mammal, including a human, in need thereof, comprising administering a pharmacologically effective amount of a compound of Claim 4.

12. A method of inhibiting aggregation of blood platelets in a mammal, including a human, comprising administering a pharmacologically effective amount of a compound of Claim 4.

13. The method as claimed in Claim 6, in which said compound is co-administered with an anticoagulant agent.

14. The method as claimed in Claim 7, in which said compound is co-administered with an anticoagulant agent.

15. The method as claimed in Claim 8, in which said compound is co-administered with an anticoagulant agent.

16. The method as claimed in Claim 6, in which said compound is co-administered with a thrombolytic agent.

17. The method as claimed in Claim 7, in which said compound is co-administered with a thrombolytic agent.

18. The method as claimed in Claim 9, in which said compound is co-administered with a thrombolytic agent.

19. The method as claimed in Claim 8, in which said compound is co-administered with a thrombolytic agent.

20. The method as claimed in Claim 6, in which said compound is co-administered with a platelet anti-aggregation agent.

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21. The method as claimed in Claim 7, in which said compound is co-administered with a platelet anti-aggregation agent.

5 22. The method as claimed in Claim 8, in which said compound is co-administered with a platelet anti-aggregation agent.

23. A pharmaceutical composition, comprising a compound as claimed in Claim 1, and a pharmaceutically acceptable carrier.

10 24. A pharmaceutical composition comprising the compounds as claimed in Claim 1, a pharmaceutically acceptable carrier and a compound taken from the group consisting of thrombolytic agents, platelet anti-aggregation agents and anti-coagulant agents.

15 25. The composition as claimed in Claim 19, in which said pharmaceutically acceptable carrier consists of a sustained release pharmaceutical formulation.

20 26. A pharmaceutical composition for inhibiting the binding of fibrinogen to blood platelets in a mammal, including a human, comprising a compound of Claim 1 and a pharmaceutically acceptable carrier.

25 27. A pharmaceutical composition for inhibiting the aggregation of blood platelets in a mammal, including a human, comprising a compound of Claim 1 and a pharmaceutically acceptable carrier.

30 28. A pharmaceutical composition for inhibiting the binding of fibrinogen to blood platelets in a mammal, including a human, comprising a compound of Claim 4 and a pharmaceutically acceptable carrier.

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29. A pharmaceutical composition for inhibiting the aggregation of blood platelets in a mammal, including a human, comprising a compound of Claim 4 and a pharmaceutically acceptable carrier.

5

30. A composition for inhibiting the aggregation of blood platelets in a mammal, including a human, comprising a compound of Claim 1 in combination with a thrombolytic agent and a pharmaceutically acceptable carrier.

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31. A composition for inhibiting the aggregation of blood platelets in a mammal, including a human, comprising a compound of Claim 1 in combination with an anti-coagulant and a pharmaceutically acceptable carrier.

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32. A composition for preventing thrombus or embolus formation in a mammal, including a human, comprising a compound of Claim 1 and a pharmaceutically acceptable carrier.

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33. A composition for preventing thrombus or embolus formation in a mammal, including a human, comprising a compound of Claim 1 in combination with a thrombolytic agent and a pharmaceutically acceptable carrier.

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34. A composition for preventing thrombus or embolus formation in a mammal, including a human, comprising a compound of Claim 1 in combination with an anti-coagulant and a pharmaceutically acceptable carrier.

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35. A composition for treating thrombus or embolus formation in a mammal, including a human, comprising a compound of Claim 1 and a pharmaceutically acceptable carrier.

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36. A composition for treating thrombus or embolus formation in a mammal, including a human, comprising a compound of Claim 1 in combination with a Thrombolytic agent and a pharmaceutically acceptable carrier.

37. A composition for treating thrombus or embolus formation in a mammal, including a human, comprising a compound of Claim 1 in combination with an anti-coagulant and a pharmaceutically acceptable carrier.

38. A composition for treating thrombus or embolus formation in a mammal, including a human, comprising a compound of Claim 1 in combination with an anti-platelet agent and a pharmaceutically acceptable carrier.

39. A method for inhibiting the aggregation of blood platelets in a mammal, including a human, comprising administering the composition of Claim 24.

40. A method for preventing or treating thrombus or embolus formation in a mammal, comprising administering the composition of Claim 25.

41. A method for inhibiting the aggregation of blood platelets in a mammal, including a human, comprising administering the composition of Claim 29.

42. A compound of Claim 1 for use in inhibiting the binding of fibrinogen to blood platelets, inhibiting the aggregation of blood platelets, treating thrombus or embolus formation, or preventing thrombus or embolus formation in a mammal, including a human.

43. A compound of Claim 2 for use in inhibiting the binding of fibrinogen to blood platelets, inhibiting the aggregation of

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blood platelets, treating thrombus or embolus formation, or preventing thrombus or embolus formation in a mammal, including a human.

5 44. A compound of Claim 3 for use in inhibiting the binding of fibrinogen to blood platelets, inhibiting the aggregation of blood platelets treating thrombus or embolus formation, or preventing thrombus or embolus formation in a mammal, including a human.

10 45. A compound of Claim 4 for use in inhibiting the binding of fibrinogen to blood platelets, inhibiting the aggregation of blood platelets, treating thrombus or embolus formation, or preventing thrombus or embolus formation in a mammal, including a human.

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US93/11623

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) : Please See Extra Sheet.

US CL : Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : Please See Extra Sheet.

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ONLINE, APS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|-----------|--|------------------------------------|
| A,P. | US, A, 5,252,586 (CAIN ET AL) 12 OCTOBER 1993, SEE COLUMN 1, LINES 1 +. | 1 - 12, 23, 26 - 29, 32, 35 AND 39 |
| A | US, A, 5,064,814 (KLEIN ET AL) 12 NOVEMBER 1991, SEE COLUMN 3, LINES 1 +. | 1 - 12, 23, 26 - 29, 32, 35 AND 39 |
| A | US, A, 4,064,255 (CHAMPSEIX ET AL) 20 DECEMBER 1977, SEE COLUMNS 1 AND 2. | 1 - 12, 23, 26 - 29, 32, 35 AND 39 |
| A | US, A, 4,122,255 (KRAPCHO) 24 OCTOBER 1978, SEE COLUMNS 1 AND 2. | 1 - 12, 23, 26 - 29, 32, 35 AND 39 |

☒ Further documents are listed in the continuation of Box C.
 ☐ See patent family annex.

| | | |
|--|-----|--|
| * Special categories of cited documents: | * T | later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention |
| * A | | |
| * E | * X | document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone |
| * L | * Y | document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art |
| * O | | |
| * P | * & | document member of the same patent family |

Date of the actual completion of the international search

11 MARCH 1994

Date of mailing of the international search report

20 APR 1994

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C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|-----------|--|----------------------------|
| A | US,A, 4,622,331 (JOZIC) 11 NOVEMBER 1986, SEE COLUMN. 1 LINES 30. | 1-12,23,26-29,32,35 AND 39 |
| A | US,A, 5,030,654 (BARNISH ET AL) 09 JULY 1991, SEE COLUMN 1 LINES 40+. | 1-12,23,26-29,32,35 AND 39 |
| A | EP,A, 0,372,486 (ALIA ET AL) 13 JUNE 1990, SEE PAGE 2. | 1-12,23,32,35 AND 39 |
| A | EP,A, 0,478,363 (LASWELL ET AL) 01 APRIL 1992, SEE PAGE 2. | 1-12,23,26-29,32,35 AND 39 |

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